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CONTENTS

OCT 21 1954

THE ROLE OF NUTRITION IN THE MANAGEMENT OF PREGNANCY:

A REVIEW OF RECENT STUDIES

William E. Josey 303

DIET AND PLASMA CHOLESTEROL LEVELS

G. A. Mayer, W. Ford Connell, Margaret S.

DeWolfe, and J. M. R. Beveridge 316

SCURVY IN ADULT AFRICANS: A CLINICAL, HAEMATOLOGICAL, AND PATHOLOGICAL STUDY

H. Grusin and P. S. Kincaid-Smith 323

THE USE OF ORALLY-FED LIQUID FORMULAS IN METABOLIC STUDIES

Edward H. Ahrens, Jr., Vincent P. Dole,

and David H. Blankenhorn 336

THE FOOD CONSUMPTION OF JUVENILE DIABETICS

EVALUATION OF DIETS USED AT HOME

AND AT SUMMER CAMP

Harry G. Jacobi 343

EDITORIALS:

Should Vitamin-Mineral Products be Standardized?

Robert S. Goodhart 348

Some Thoughts Regarding Obesity

Laurance W. Kinsell 350

DIETOTHERAPY: The Low Cholesterol, Low Fat Diet

Corinne H. Robinson 353

DEPARTMENTS

ABSTRACTS OF CURRENT LITERATURE: Infant Feeding; Bifidus Factor;

Protein Nutrition; Alcohol; Nutritional Aspects of

Antibiotics; Iron; The Roles of Vitamin B₁₂; Lipids;

Items of General Interest 362

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The American Journal of Clinical Nutrition

SEPTEMBER-OCTOBER 1954

VOLUME 2, NUMBER 5

CONTENTS

THE ROLE OF NUTRITION IN THE MANAGEMENT OF PREGNANCY:

A REVIEW OF RECENT STUDIES

William E. Josey 303

No one doubts that good nutrition is important in pregnancy—but *how* good must it be, and *how* important is it? That poor nutrition may cause or contribute to the various disorders of pregnancy is generally admitted—but here the evidence is more contradictory and must be carefully assessed. More debatable still is the possible influence of maternal deficiencies in the production of fetal abnormalities—demonstrable in animals, but not proved in humans. Our prize-winning essay examines the recent literature for clues to all these mysteries, and goes on to discuss dietary and vitamin requirements and the altered mineral metabolism in normal and abnormal pregnancy.

DIET AND PLASMA CHOLESTEROL LEVELS

G. A. Mayer, W. Ford Connell, Margaret S. DeWolfe, and J. M. R. Beveridge . . . 316

Attempts to isolate the effects of dietary cholesterol from those of dietary fat (usually ingested simultaneously) continue to be made. In this Canadian study, more evidence is accumulated on the significant role of animal fat and the relative innocence of cholesterol in raising plasma cholesterol levels.

SCURVY IN ADULT AFRICANS:

A CLINICAL, HAEMATOLOGICAL, AND PATHOLOGICAL STUDY

H. Grusin and P. S. Kincaid-Smith 323

Full-blown scurvy is now rare in the United States; unfortunately, it remains a problem in many other regions of our malnourished world. This very interesting and important study—the first, to our knowledge, to deal with “chronic scurvy”—presents thirty cases of scurvy in African subjects and indicates that long-term vitamin C deficiency may be the cause of some instances of isolated hemorrhage observed in this population.

THE USE OF ORALLY-FED LIQUID FORMULAS IN METABOLIC STUDIES

Edward H. Ahrens, Jr., Vincent P. Dole, and David H. Blankenhorn 336

The difficulty of performing accurate balance studies when mixed natural foods are fed makes the development of constant intake techniques a matter of great practical value. The authors present their unusually successful solution of this problem, achieved by the oral feeding of well-tolerated homogenized formulas. Equipment, methods of preparation, and types of metabolic study in which these formulas have proved useful are detailed, making this a very valuable guide for clinicians faced with similar problems.

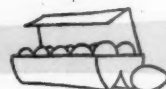
Contents continued on page v

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The American Journal of Clinical Nutrition

SEPTEMBER-OCTOBER 1954

VOLUME 2, NUMBER 5

Contents continued from page iii

THE FOOD CONSUMPTION OF JUVENILE DIABETICS.

EVALUATION OF DIETS USED AT HOME AND AT SUMMER CAMP

Harry G. Jacobi 343

In the third of a series of studies on young diabetics, data are presented on the home diet of these children, and its deviation from the prescribed diet and from the diet formulated for them at a summer camp for diabetic children. The moral of this report is implicit in the author's observation that, in a large percentage of cases, neither the children nor their parents had ever received proper dietary instructions. Ignorant of food values, many of the children were being controlled on unnecessarily high doses of insulin, which could have been reduced by adherence to a correctly designed diet.

EDITORIALS:

Should Vitamin-Mineral Products Be Standardized?

Robert S. Goodhart 348

Some Thoughts Regarding Obesity

Laurance W. Kinsell 350

DIETOTHERAPY: The Low Cholesterol, Low Fat Diet

Corinne H. Robinson 353

DEPARTMENTS 356

ABSTRACTS OF CURRENT LITERATURE: Infant Feeding; Bifidus Factor;

Protein Nutrition; Alcohol; Nutritional Aspects of Antibiotics; Iron;

The Roles of Vitamin B₁₂; Lipids; Items of General Interest 362

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SEPTEMBER-OCTOBER 1954

VOLUME 2, NUMBER 5

The Role of Nutrition in the Management of Pregnancy:

*A Review of Recent Studies**

By WILLIAM E. JOSEY, M.D.[†]

THE AIM of modern obstetrics is to provide the best possible maternal care in the interest of both mother and child. Toward the achievement of this end, proper nutrition during pregnancy has been accorded a deservedly prominent role. Since the study of nutrition as it relates to pregnancy is by no means a static field of investigation, it is important that this principle in obstetric management be re-evaluated periodically.

The purpose of this paper is to present a review of the pertinent literature for the period 1950-53. The bibliography, while not intended to be exhaustive, is fairly comprehensive for the designated years. Additionally, reference is made to some reports that antedate this interval and to others that have appeared subsequently. The earlier work has been reviewed by Garry and Wood¹ and by Burke and Stuart.²

From the University Hospital, Augusta, Ga.

*This paper was awarded First Prize in the recent essay contest for internes and residents sponsored by this JOURNAL. The author, a graduate of the Medical College of Georgia in 1953, is presently a resident in obstetrics at the Johns Hopkins Hospital, Baltimore.

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STUDIES OF THE RELATIONSHIP OF MATERNAL NUTRITION TO THE COURSE AND OUTCOME OF PREGNANCY

Numerous studies have purported to show that faulty nutrition bears a relationship to various abnormalities of pregnancy. Several investigators have also attempted to relate fetal development and condition of the newborn to the maternal nutritional status. Authorities now caution, however, against regarding nutrition as an isolated etiological factor in pregnancy and neonatal disorders. Scrimshaw³ called attention to the fallacy of attributing pregnancy complications to dietary deficiencies alone. This is further emphasized by McGanity,⁴ who points out that the influence of nutrition on one such abnormal condition must take into account the interrelationships with associated abnormalities.

Burke and her colleagues at the Harvard Medical School have promoted the concept that prenatal nutrition is intimately related to the course and outcome of pregnancy. However, in contrast to their work is that of others such as the Vanderbilt group, who in their recent nutritional investigations⁵ came to the conclusion that there was no clear-cut indication that maternal dietary deficiencies

could be linked to the wide variety of obstetric and fetal abnormalities studied.

Following is a summation of other recent studies of the effect of nutrition on the maternal and fetal outcome.

Effect of Nutrition on the Maternal Outcome

Douglas and Scadron⁶ investigated the influence of obesity in pregnancy. In a series of 521 patients weighing over 200 pounds, they found that overweight predisposed to hypertension and toxemia and resulted in an increased incidence of shoulder impaction during delivery and postpartum hemorrhage. The latter two complications were attributed to the greater infant size. There was no statistical effect on the occurrence of prolonged labor and abnormal fetal presentations or on maternal and fetal mortality.

Abnormal weight gain during pregnancy is generally regarded as a premonitory sign of trouble. Indeed, Dieckmann⁷ believes that too rapid or excessive weight gain is of more significance in the diagnosis of toxemia than hypertension and proteinuria. Nevertheless, Alexander and Downs,⁸ in a review of 1000 private patients, concluded that weight gain has no effect on length of labor and little, if any, on the development of toxemia. However, in his discussion of this paper, Bailey⁹ considered it significant that *all* patients in this series who developed toxemia (3 per cent) had a greater-than-average weight gain. In addition, he pointed out that of those with above average weight gain, one in three had longer-than-average labor; whereas of those with below average gain, only one in five had extended labor.

An elaborate investigation of weight and weight gain was reported by Tompkins and Wiehl.¹⁰ They found that the incidence of premature labor was significantly increased in patients who were 20 per cent or more underweight at the beginning of pregnancy. Surprisingly, the incidence of toxemia was greater in patients whose initial weight was *either* 20 per cent or more above or 20 per cent or more below normal. They believe that initial underweight and/or inadequate weight gain predispose to premature labor, while the mech-

anism for toxemia is considered to be mainly excessive weight gain during the second and third trimesters. The average normal weight gain of their patients was 24 pounds. They further believe that both underweight and overweight may be indicative of a nutritional deficiency state, the former obviously being more important in this respect. They were able to demonstrate a lessened incidence of toxemia and premature labor in patients who received protein and vitamin supplements in addition to a basic diet.

Another relationship brought out in this study was the influence of anemia in predisposing to premature labor. It was suggested that this might be due to the effect of anoxia.

The influence of anemia on labor has received little attention. Traylor and Torpin¹¹ reviewed the literature and found but a few references to the subject. In a series of 1019 pregnancies, they showed that the incidence of prolonged labor (over 24 hours) was significantly greater in women whose hemoglobin was less than 11 Gm./100 ml. A similar finding has been reported by Zilliacus and Putkinen.¹²

Toverud¹³ reported the results of a program of supervised prenatal care that was introduced in Oslo, Norway, in 1938. Evidence was obtained indicating that dietary supervision reduced the incidence of prematurity as compared with an unsupervised control group. Furthermore, it was felt that the supervised women were better able to breast feed their babies.

The influence of undernutrition in reducing the ability of the mother to lactate was also shown by Dean¹⁴ in an analysis of the records of German obstetric clinics during the war years from 1937 to 1948.

Block and his co-workers¹⁵ found the incidence of prematurity to be more related to socioeconomic than to obstetric factors and they, too, concluded that prematurity is primarily a nutritional problem. This and the preceding findings with respect to prematurity are in agreement with the work of Burke and associates,¹⁶ who in 1949 reported that all but one of the premature infants in a series of 68 were born to mothers on inadequate diets.

By contrast, Speert, Graff, and Graff¹⁷ studied the dietary intakes and blood hematological and biochemical values of 70 mothers who delivered premature infants, using as a control 67 who had full term babies, and were unable to demonstrate a relationship between dietary deficiency and prematurity.

Dieckmann and his associates¹⁸ investigated the effect of protein consumption on the course of pregnancy and found no relation to toxemia, premature labor, or prolonged labor. However, low protein diets were correlated with an increased incidence of abortion and anemia.

Scrimshaw,³ in a study of 10,000 women in Panama, also could demonstrate no relationship between low protein intake and toxemia. Although adequacy of diet was found to parallel socioeconomic level, there was no significant difference in incidence of toxemia between the high and low income groups.

Ferguson and Hinson¹⁹ favor the viewpoint that inadequate protein intake is causally related to toxemia. In a survey of protein consumption among clinic patients at the Charity Hospital in New Orleans, they found the diets of these women, who have a high rate of toxemia, to be markedly deficient in protein.

An interesting investigation carried out at the Women's Hospital, Sydney, Australia, was reported by Hamlin.²⁰ From 1936 to 1948, at that institution, the average incidence of eclampsia was 1 in 350. During the latter year a drive was begun which resulted by 1950 in no cases of eclampsia in 5000 consecutive patients. The formerly high rate of eclampsia was correlated with the high carbohydrate, low protein diet prevalent among Australian women. The attack consisted primarily of instituting a high protein, high vitamin, low carbohydrate regimen before mid-pregnancy and watching carefully for early signs and symptoms of pre-eclampsia. Considerable emphasis was placed on the benefit of the dietary adjustments.

Although the evidence for a nutritional role in the pathogenesis of toxemia is inconclusive, it is nevertheless impressive. Thus, proponents of the major theories of the etiology of toxemia regard faulty nutrition as a predisposing

factor if not a direct causal factor. A widely held theory, for which Page²¹ is a leading advocate, postulates uterine ischemia due to local mechanical factors (labor, multiple pregnancy, hydramnios, etc.), hormonal factors, or impaired general circulation (hypertension, nephritis, anemia, etc.). It is believed that the resultant placental injury allows the release of a pressor substance mediating development of the toxemic syndrome. Nutritional factors are presumed to exert an influence on the basis either of anemia and associated hypoxia or of impaired placental nutrition as a result of vitamin deficiencies.

The point of view that hypoxia on an anemic basis could account for placental ischemia has received support recently in an investigation conducted by Berlin and his associates.²² Using p³² labeled red blood cells they showed that the total red cell volume is below normal and confirmed previous reports that the plasma volume is reduced in pre-eclamptic women.

Bartholomew²³ has long expounded the hypothesis that a toxin is released by the breakdown of placental infarcts. This theory stems from the fact that such infarcts occur with greater frequency in placentas of toxemic patients, though most authorities on the placenta regard this circumstance as a result of the condition rather than a cause.²⁴ Bartholomew and Kracke²⁵ related placental infarction to the hypercholesteremia of pregnancy. However, Moses and his co-workers²⁶ were unable to demonstrate any changes in serum cholesterol of pregnant women on high cholesterol diets, nor was there any increase in observed vascular lesions or infarctions in the placentas of these women.

Following the suggestion by Smith and Smith²⁷ and Selye²⁸ that eclampsia may belong to the group of "diseases of adaptation," several investigators have become interested in applying Selye's concept of stress and adrenal dysfunction to the study of toxemia. Evidence for this theory includes the known hypertrophy of the adrenal glands and increase in adrenal corticoid production during pregnancy, and the fact that kidney lesions (nephrosclerosis) similar to those found in

eclampsia can be produced in experimental animals by the administration of desoxycorticosterone. It is postulated that failure to adjust to the physiological stresses of pregnancy leads to increased corticoid activity, which in the presence of excess sodium in the diet results in sodium retention and edema.²⁰

Evidence has accumulated indicating that dietary measures are of considerable importance in influencing the course of the diseases of adaptation.²³ Hence, advocates of the stress theory have inferred that nutritional factors enter into the pathogenesis of toxemia either by contributing to altered adrenal function³⁰ or by aggravating the harmful effects of such altered function.^{31,32} For speculation along these lines, the reader is referred to the writings of Parviainen and associates,^{29,33} Patterson,³⁰ and Garrett.^{31,32}

Effect of Nutrition on the Fetal Outcome

In 1949 Burke and her associates¹⁶ reported their observations on the relationship of maternal nutrition to the condition of the newborn infant. Maternal diets rated as "excellent" were associated with 95 per cent healthy babies, while inferior diets were associated with 65 per cent of the babies in poor condition. Most of the neonatal deaths and congenital defects were found in infants whose mothers were considered to have had inferior prenatal diets.

In a survey of the records of German obstetric clinics from 1937 to 1948, Dean¹⁴ was unable to relate undernutrition to the incidence of stillbirths or congenital malformations. However, undernutrition apparently did cause an average decrease in birth weights.

In Dieckmann's¹⁸ investigation of the influence of protein consumption in pregnancy it was observed that high protein diets resulted in healthier infants.

The effect of maternal obesity in increasing the size of the infant, as demonstrated by Douglas and Scadron,⁶ has been mentioned.

Smith, Worcester, and Burke³⁴ have studied the effect of maternal diet on size and content of the fetal liver. From their results they concluded that the weight and composition of the fetal liver reflect the maternal intake during

pregnancy and presumably can be altered by improving the mother's diet.

The production of congenital malformations in experimental animals by inducing maternal vitamin deficiencies has been under investigation for a number of years. Recently, deficiency of folic acid was added to the list of avitaminoses capable of causing abnormalities in the young of female rats.³⁵

Wilson and Warkany³⁶ have compared the experimental cardiovascular anomalies produced in the offspring of vitamin A-deficient rats with similar malformations in the human. They suggest that both genetic and environmental factors may adversely affect normal cardiovascular development.

The Vanderbilt group⁵ were unable to obtain evidence for deficiency diseases in the mothers of malformed infants in their series.

NUTRITIONAL REQUIREMENTS IN PREGNANCY AND LACTATION

The daily dietary allowances for pregnant and lactating women, as recommended by the Food and Nutrition Board of the National Research Council (1948 revision),³⁷ are given in Table I.

TABLE I
Daily Allowances Recommended by the Food and Nutrition Board of the National Research Council for Pregnancy and Lactation, Compared with Those for the Normal Nonpregnant Woman (1948)

Nutrients	Normal (moderately active woman)	Pregnancy (latter half)	Lactation
Calories	2400	2400	3000
Protein (Gm.)	60	85	100
Calcium (Gm.)	1.0	1.5	2.0
Iron (mg.)	12	15	15
Vitamin A (I.U.)	5000	6000	8000
Thiamine (mg.)	1.2	1.5	1.5
Riboflavin (mg.)	1.5	2.5	3.0
Niacin (mg.)	12	15	15
Ascorbic acid (mg.)	70	100	150
Vitamin D (I.U.)	—	400	400

It should be pointed out that these allowances were compiled by the National Research Council on the basis of concurrent knowledge of essential nutrients. Burke² stresses that they should be used only as a guide to estab-

lishing adequate nutrition during gestation and lactation. Moreover, the problem is possibly more complex than can be solved merely by the provision of a diet planned to meet the minimum requirements. Tompkins,³⁸ for example, believes that the stress of pregnancy creates an added demand which must be met by dietary supplementation in those women entering pregnancy with a deficient "nutritional reserve." Since there is no way as yet of ascertaining the maternal nutritional reserve status, he recommends routine poly-vitamin supplementation. However, though widely practiced, dietary supplementation is not advocated by all authorities. Darby³⁹ is of the opinion that it is unnecessary unless a specific deficiency exists.

Tompkins goes still further and raises the question of a possible hereditary influence on woman's capacity to adjust to the increased nutritional demands of pregnancy. It has been postulated by Williams, Beerstecher, and Berry⁴⁰ that some individuals are genetically predisposed to the development of nutritional deficiencies and thus require larger intakes of essential substances than do normal people. If this is true, as Tompkins suggests, it is obvious that the dietaries of pregnant women should be individualized. Of course, at the present time one can only speculate as to the importance of this mechanism in maternal deficiency states.

Protein

There is general agreement that the protein requirement of pregnant women is considerably more than that of nonpregnant women. The National Research Council recommends an average daily allowance of 85 Gm. during the latter half of pregnancy, an increase of 25 Gm. over the recommended allowance for the moderately active nonpregnant woman.

Reference has been made to the investigation by Dieckmann and his associates¹⁸ of the relationship of protein intake to the health of the mother and baby. It was found that low protein diets predisposed to abortion and resulted in a greater incidence of anemia. There was, too, a correlation between increased protein consumption and healthy babies.

Most of the recent work has centered on the controversy regarding the influence of protein in the causation of toxemia of pregnancy. Several of these studies have already been mentioned. Though efforts to relate toxemia to protein deficiency have been only partially successful, the known alterations in the normal pattern of plasma protein concentrations in toxemia are regarded by many as indicative of an associated disturbance of protein metabolism. Mack and his co-workers⁴¹ have re-evaluated the plasma proteins in toxemia using the electrophoretic method. Their results confirmed previous reports that there are changes in the plasma proteins, such as decreased total protein and albumin, which are modifications of the normal physiologic changes of pregnancy.

Since there is evidence for disturbed liver function in toxemia, these workers⁴² have also analyzed the plasma proteins in five cases of hepatic disease complicating pregnancy. However, they found that the hyperglobulinemia of cirrhosis is much greater than that of normal or toxic pregnancy and concluded that toxemia is not regularly accompanied by this evidence of liver damage.

Normally during pregnancy there is a marked storage of protein, as indicated by nitrogen balance studies. Mukherjee and Govan⁴³ have shown that when toxemia supervenes the storage of nitrogen practically ceases, and a negative nitrogen balance ensues because of the loss of protein in the urine. They were unable to state whether the cessation of nitrogen storage is due to increased protein catabolism or to inability to utilize the assimilated protein.

Because of the importance of choline and methionine in protein metabolism, Sims⁴⁴ felt that a study of the excretion of these substances in pregnancy might shed light on the role of protein in toxemia. However, he found no significant difference between choline and methionine excretion in normal and toxic pregnancies.

Vitamins

Vitamin A. Barnes⁴⁵ has studied the placental metabolism of vitamin A. He con-

cluded that, since the fetus obtains its vitamin A in the form of carotene, a fetal deficiency could be due to either long-standing maternal depletion or to failure of the fetal mechanism of converting carotene to vitamin A.

The possibility that maternal vitamin A deficiency may be a factor in certain congenital abnormalities has been mentioned.

Vitamin B Complex. The therapeutic value of the B-complex vitamins in nausea and vomiting of pregnancy is well known. Thiamine and pyridoxine are said to be particularly effective in combatting hyperemesis.²⁴ Of the B-complex group, thiamine, riboflavin, and nicotinic acid are known to be essential to human nutrition.

Thiamine and Riboflavin. On the basis of dietary intakes, excretions, and test dose returns in pregnant and nonpregnant women, Oldham, Sheft, and Porter⁴⁶ did not find the requirements for thiamine and riboflavin to be increased in pregnancy. The results of this study are not in agreement with previous work on these vitamins nor with a recent investigation of the riboflavin requirement in pregnancy by Brzezinski and his colleagues.⁴⁷

The condition known as polyneuritis of pregnancy is thought to be a manifestation of thiamine deficiency. Eiseman⁴⁸ has called attention to the similarity between the clinical findings in polyneuritis and those of postpartum and postoperative thrombophlebitis; namely, leg pain, Homans' sign, and increase in circumference of the calf. He suggests that the increased requirement for thiamine postpartum and postoperatively may occasionally be responsible for the development of these symptoms and signs, which could easily be mistaken for manifestations of thrombophlebitis. The diagnosis of polyneuritis due to thiamine deficiency can readily be established by the response to large doses of thiamine.

Nicotinic Acid. The metabolism of nicotinic acid in pregnancy has been re-examined by Lojkin, Wertz, and Dietz.⁴⁹ It was confirmed that women on self-selected diets excrete nicotinic acid metabolites in amounts exceeding the niacin intake and that available from tryptophan intake.

Pyridoxine. Although pyridoxine is not included among the essential vitamins for which the requirements have been ascertained, recent work by Wachstein and Gudaitis^{50,51,52} provides evidence that the need for this vitamin is increased during pregnancy. This conclusion is based on studies of pyridoxine metabolism by means of a vitamin B₆ load test and the urinary excretion of xanthurenic acid following administration of 10 Gm. of *dl*-tryptophane. The latter test has been shown to be indicative of pyridoxine deficiency in the human. Their findings suggest that 10 mg. of pyridoxine daily will cover the increased demand in pregnancy.

On the other hand, Beaton and his co-workers⁵³ came to the conclusion that the need for pyridoxine may be decreased in pregnancy. They assumed the metabolite 4-pyridoxic acid to be the principal end-product of vitamin B₆ metabolism and found that the urinary excretion of this substance is decreased in pregnant women. Their results were interpreted as evidence that pyridoxine is required in smaller amounts during pregnancy.

Using the xanthurenic acid excretion test mentioned above, Sprince and associates⁵⁴ related toxemia of pregnancy to pyridoxine deficiency by showing that the excretion of xanthurenic acid is markedly increased in toxemic patients. They suggest that the altered protein metabolism in toxemia may increase the need for pyridoxine.

A relationship between pyridoxine and the production of ovarian hormones was demonstrated experimentally by Nelson, Lyons, and Evans,⁵⁵ who were able to maintain pregnancy to the 17th day of gestation in pyridoxine-deficient rats by daily injections of estrone and progesterone. Without therapy, only 10 per cent of the pyridoxine-deficient pregnancies progressed to the 17th day.

Vitamins C and P. It is convenient to consider vitamins C and P together because both apparently are capable of strengthening capillary resistance, a property that may prove to be of value in preventing abortion. Greenblatt⁵⁶ has been impressed by the frequency of signs of capillary fragility in habitual

aborters and reports eight years' experience in treating these women with vitamin C and hesperidin (a vitamin P-like substance) in addition to the usual therapeutic regimen. He claims results that are superior to what is ordinarily expected in attempting to prevent abortion. Using the Rumpel-Leede test, and later the petechiometer, he obtained positive tests for capillary fragility in over 80 per cent of his patients classified as habitual aborters. Additional support for the rationale of vitamin C and hesperidin therapy in habitual abortion has been provided recently in a report by Javert.⁵⁷

Merkel⁵⁸ has used vitamin C with menadione bisulfite (vitamin K) in treating nausea and vomiting of pregnancy. He postulates that this therapy is beneficial because it decreases capillary permeability and lessens the chance for transfer of a "vomiting factor" to the mother.

In anemic patients with poor response to iron therapy, vitamin C is believed to aid the absorption of orally administered iron.⁵⁹

There is evidence that vitamin C deficiency plays a part in the macrocytic anemia of pregnancy. This question will be considered along with the discussion of vitamin B₁₂ and folic acid.

Vitamin E. As Goldsmith and Gibbens⁶⁰ state, "no claim for a role of vitamin E in human nutrition has yet been substantiated." The suggestion has been made that a deficiency of vitamin E, or alpha tocopherol, may be a factor in habitual abortion and other pregnancy complications. Wheat germ oil, a source of vitamin E, has been reported to have some value in treating threatened abortion, premature labor, and toxemia.⁶¹ However, there is evidence that any benefit obtained from the use of this substance cannot be attributed to its vitamin E content. Levin⁶² has called attention to the need for distinguishing between wheat germ oil and tocopherol. Although wheat germ oil has been shown to possess estrogenic, androgenic, and gonadotrophic activity, attempts to demonstrate hormonal activity following tocopherol administration have been unsuccessful.^{63,64,65}

Furthermore, no evidence for an etiological relationship between vitamin E deficiency and pregnancy complications was found by Scrimshaw, Greer, and Goodland⁶⁶ in their study of serum vitamin E levels in pregnant women.

Serum vitamin E concentrations in the newborn have been reported by Moyer,⁶⁷ who found no difference between the levels of term and premature infants. Wright, Filer, and Mason⁶⁸ confirmed this finding but showed that the prematures rapidly develop a vitamin E deficiency on artificial diets. They believe that the placental transfer of vitamin E is rather limited. György, Cogan, and Rose⁶⁹ offered further evidence for a physiological deficiency of vitamin E in newborn infants by demonstrating that administration of the vitamin blocks the tendency for the red cells of the newborn to hemolyze when exposed to a dilute solution of hydrogen peroxide.

Vitamin K. Although there is still some disagreement as to the efficacy of prophylactic antenatal administration of vitamin K, Eastman²⁴ recommends it as a routine precaution against hemorrhagic phenomena in the newborn. The usual practice is to give vitamin K to the mother as she approaches term or when she goes into labor.

Recently, several investigators^{70,71,72} have experimented with the use of vitamin K in conjunction with progesterone as an aid in preventing erythroblastosis fetalis. The rationale is considered to be similar to that mentioned above for the treatment of nausea and vomiting of pregnancy with vitamins C and K; that is, effecting a decrease in placental capillary permeability and thus affording resistance to the passage of fetal red cells across the placental barrier. The results, while not imposing, are sufficiently impressive to warrant further study.

Javert⁵⁷ includes vitamin K (in addition to vitamin C and hesperidin) in his regimen for treating habitual abortion.

Folic Acid and Vitamin B₁₂. The importance of folic acid in pregnancy has been shown by the deleterious effect of aminopterin (a folic acid antagonist) on decidual development in rats⁷³ and on maintenance of pregnancy in the rat⁷⁴ and the human.⁷⁵

The production of congenital abnormalities in the offspring of folic acid-deficient rats³⁹ was mentioned previously.

At the present time, folic acid is generally regarded as the treatment of choice in the macrocytic megaloblastic anemia of pregnancy. The literature abounds with reports of its successful use in this condition after little or no response to liver and/or vitamin B₁₂.⁷⁶⁻⁸¹ Though not uncommon in various other parts of the world, this type of anemia is rare in the United States. Darby⁵ states that folic acid is not necessary as a supplement in the presence of a normal diet.

It is reasonable to presume that women who develop megaloblastic anemia of pregnancy are suffering from a multiple deficiency. Because of the likelihood of an associated iron deficiency anemia, the adjunctive employment of iron therapy has been recommended.^{82,83}

There is evidence that the etiology of megaloblastic anemia of pregnancy is more complex than the simple deficiency of folic acid. In 1950, Patel and Kocher⁸⁴ reported the successful use of vitamin B₁₂ therapy. They discovered that, although there was poor response to vitamin B₁₂ with the usual dose required for remission in Addisonian pernicious anemia (1 µg./day), good results were obtained when at least 4 µg./day was given. This work was confirmed by Chaudhuri.⁸⁵

Holly⁸⁶ was able to bring about complete remissions in three patients by employing a combination of vitamin B₁₂ and ascorbic acid. He suggested that ascorbic acid may be necessary for the conversion of folic acid to citrovorum factor, which is regarded as the biologically active derivative of folic acid. May, Hamilton, and Stewart⁸⁷ attempted to confirm this concept by experiments in monkeys. Their results led them to conclude that, while ascorbic acid does not appear to be essential to the formation of citrovorum factor from folic acid, this conversion is more efficient in the presence of adequate amounts of vitamin C.

Girdwood⁸⁸ reviewed the literature on vitamin B₁₂ and folic acid and concluded that both are essential to normal erythrocyte maturation.

Vitamin D. According to Eastman,²⁴ the ordinary diet does not contain enough vitamin D to meet the requirement in the latter half of pregnancy and during lactation (400 I.U.). Therefore, because of its importance in calcium and phosphorus metabolism, vitamin D probably should be administered as a supplement to the prenatal diet.

Minerals

Iron. Burke and Stuart² state that the recommended iron allowance of 15 mg. is valid only if the woman enters pregnancy with an adequate iron reserve and a normal hemoglobin. Hamilton, Higgins, and Alsop⁵⁹ stress that most women are in a state of precarious iron balance at this time due to periodic menstrual bleeding, often superimposed on iron deficiency from birth and/or as a result of inadequate iron in the diet.

The importance of positive maternal iron balance for preventing anemia in newborn infants is revealed by the studies of C. A. Smith and collaborators.⁸⁹ In their work on transplacentally acquired iron in infants, they showed by the use of radioactive iron that the child's dietary iron is unimportant in hemoglobin synthesis during the first six months of life. Furthermore, from 60 to 90 per cent of the iron present in the hemoglobin at birth is still being used at the age of two years. N. J. Smith and Rosello⁹⁰ actually observed some cases of anemia in infants that resulted from inadequate iron storage *in utero*.

That large doses of iron offer no advantage over smaller doses in the treatment of iron deficiency anemia was emphasized by Hahn and his associates,⁹¹ who demonstrated that the efficiency of iron absorption is increased in pregnancy. For accurate appraisal of the response to iron therapy, Lund⁹² believes that calculation of the total hemoglobin mass (plasma volume x hemoglobin) is necessary.

When cases of anemia refractory to oral iron are encountered, Hamilton⁵⁹ recommends a trial using vitamin C and hydrochloric acid to aid absorption. If this does not prove to be efficacious, the so-called "mucosal block" may be hindering absorption. In such cases the use of intravenous iron is justified. The in-

travenous route has also been shown to be valuable in treating patients who present themselves late in pregnancy, when time is a factor.⁹³

The currently popular use of a molybdenum-iron complex in the prophylaxis and treatment of anemia has been questioned by Gullberg and Vahlquist,⁹⁴ who were not able to demonstrate any increase in iron absorption using this preparation, and by Darby,⁹⁵ who suggested a possible toxic effect of molybdenum. Nevertheless, the clinical experience of one group has indicated that molybdenized iron may be better utilized than simple iron salts.^{96,97}

According to Berk, Burchenal, and Castle,⁹⁸ there is no justification for the use of cobalt as an adjunct to iron therapy. Also, it is questionable whether cobalt is of any benefit in refractory anemias.

Calcium and Phosphorus. The greatest need by the fetus for calcium is during the last month of gestation. Consequently, the mother must obtain adequate stores of calcium earlier in pregnancy in order to withstand the fetal demand at this time. Adequate amounts of phosphorus are supplied if the protein intake is satisfactory.²⁸

Doubt has been cast on the advisability of the practice of supplementing the diet with preparations containing dicalcium phosphate. Page and Page⁹⁹ related leg cramps in pregnancy to a low serum ionized calcium and presented evidence suggesting that the administration of a combination of calcium and phosphorus lowers this level and thus contributes to the development of cramps. They claim to have been able to produce leg cramps by prescribing dicalcium phosphate. The work of Gross, Wager, and Loving¹⁰⁰ and that of Leichsenring and co-workers¹⁰¹ provide additional evidence that phosphorus inhibits the utilization of calcium. The immediate practical interpretation of these findings is uncertain at present.

Sodium and Potassium. The use of the low sodium diet to counteract sodium retention and edema is a cardinal principle in the prophylaxis and treatment of toxemia of pregnancy. Despite recent advances in our knowl-

edge of potassium metabolism, little attention has been directed to the role of potassium in the disturbed physiology of toxemia, as pointed out by Turner and Fair.¹⁰²

There is reason for believing that the study of sodium and potassium metabolism in toxemia may contribute to a better understanding of this enigmatic condition. Parviainen and his associates³³ maintain that toxemia is characterized by intracellular penetration of sodium, replacing some of the potassium normally contained within the cells. On this basis, Garrett³² has suggested that most of the severe signs and symptoms in toxemia may result from this intracellular electrolyte shift. On the other hand, there is also evidence that potassium is retained in this condition.¹⁰²

Perhaps further investigation will clarify the role of sodium and potassium in the physiological disturbances that characterize toxemia of pregnancy. Since the chief source of potassium is food, it is not inconceivable that adjustments in the dietary intake of this element will be found to have, as in the case of sodium, a beneficial influence on the course of this obstetrical complication.

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RESUMEN

*El papel de la nutrición en el embarazo.
Revista de estudios recientes*

Se pasa revista a la literatura aparecida durante el período 1950-1953. Se discute la relación entre la mala nutrición y las diversas anomalías del embarazo, así como la repercusión del estado nutricional de la madre sobre el desarrollo del feto y la condición del recién nacido. Se refiere la evidencia acumulada sobre el efecto de un peso inicial deficiente o excesivo de la madre, o de una ganancia excesiva de peso durante el embarazo, en determinar una mayor frecuencia de toxemia y prematuridad. Se discute también la influencia de la anemia inicial sobre la duración del parto y el papel de la buena nutrición en favorecer el amamantamiento.

Se consideran los requerimientos dietéticos de la mujer encinta, sobre todo en lo que concierne la proteína. Se examina en seguida el valor de las diversas vitaminas en la profilaxis y terapia de los muchos trastornos del embarazo (náusea, polineuritis, aborto, anemia, etc.). Finalmente se discuten las alteraciones determinadas por el embarazo normal y anormal en el metabolismo de los minerales: hierro, sodio, calcio, y potasio.

Diet and Plasma Cholesterol Levels

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THE ROLE of diet in affecting plasma cholesterol levels in experimental animals has been clearly demonstrated in certain species.¹⁻⁴ This picture is to be contrasted with that found in studies with humans, which have been marked by many conflicting reports and controversies regarding the interpretation of the data obtained. On the one hand, a number of investigators have reported that alteration of dietary cholesterol level has no effect on the plasma content of this lipid,^{5,6} and, on the other hand, Messinger *et al.*⁷ have claimed that increased dietary cholesterol levels do in fact bring about increased plasma concentrations of this substance. However, these workers also indicate that some other dietary factor present in egg yolk has an important determining influence.

The level of dietary fat has also been implicated in studies utilizing both experimental animals^{8,9} and humans.^{10,11} There would appear to be a reasonable degree of consistency in the reports on the effect of high levels of animal fat in elevating plasma cholesterol concentrations. At the same time, it must be pointed out that animal fat has invariably associated with it a significant percentage of cholesterol, and hence the possibility exists that the alteration may have been due to this circumstance. There have been conflicting results reported on the effect of high levels of

vegetable fat. Kinsell *et al.*,¹² working with various hospital patients who were receiving a variety of treatments, including ACTH and cortisone, both of which have been noted to affect plasma lipids under certain conditions,¹³ reported that diets containing high levels of vegetable fat not only did not lead to increased plasma cholesterol levels but actually effected a decrease. Groen and his colleagues,¹⁴ in a long-term investigation using sixty presumably normal subjects, also noted a decrease when a diet essentially free from cholesterol (estimated intake about 1.5 mg./day) and high in vegetable fat was substituted for one high in animal fat. Conflicting conclusions, however, have been reached by Hildreth, Mellinkoff, Blair, and Hildreth,¹¹ and by Keys.⁵ It seems obvious that certain important factors affecting plasma lipid levels are not being properly controlled in these studies. The possibility of such factors as positive or negative calorie balance,^{15,16} physical or emotional stress,^{13,14} and the various types of vegetable fats has not always been adequately taken into consideration. These and other unknown influences may well serve to resolve the conflicting reports and opinions on this subject.

In the study herewith described, dietary modifications were made with a view to altering the level of natural cholesterol, or animal or vegetable fat, at the expense of primarily carbohydrate foods. The latter were taken in amounts sufficient to satisfy the appetite and to maintain body weight as constant as possible.

EXPERIMENTAL

Methods

The co-operation of five dependable and apparently healthy and emotionally stable

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male subjects (physicians and internes) was obtained. Complete physical examinations and electrocardiograms were carried out and found to be negative. No ill effects of a physical or emotional nature were observed throughout the experimental period. The subjects had been in a state of nutritional balance, without overt weight gain or loss for three to four months prior to our study.

All five subjects ate for some months prior to and during the experimental period in a common dining-room. For each individual the composition of the pre-experimental and subsequent experimental diets was calculated as accurately as possible by Miss F. M. Silverlock, chief dietitian of the Kingston General Hospital, using Bridge's *Food and Beverage Analyses* (1950) by Mattice. All diets were prepared under her direction.

TABLE I

Approximate Composition of the Daily Diet Prior to Our Experiments

Subject	Protein	Fat	Carbohydrates	Cholesterol	Total calories	Calories taken as fat
	Gm.	Gm.	Gm.	mg.		%
A	80	80	240	500	2000	34
B	120	140	315	300	3000	42
C	100	120	180	500	2200	33
D	130	150	210	800	2700	50
E	140	150	190	1000	2700	50

The intake of cholesterol, and of animal and vegetable fat, was controlled as closely as possible. Some leeway was permitted in the intake of carbohydrate foods such as potatoes, sugar, marmalade, bread, and arrowroot biscuits, the principal objective being to maintain body weight fairly constant. Blood samples were taken prior to breakfast at appropriate intervals throughout the experimental period, and total and free cholesterol were determined on the plasma by the Schoenheimer-Sperry procedure.¹⁷ The characteristics of the experimental rations and the order in which they were eaten are given below.

Diet No. 1

This ration, which was ingested for a period of four weeks, was made low in fat and in cholesterol by the partial elimination of vege-

table and animal fat with associated cholesterol. Table II gives the approximate composition of the modified diet; it may be noted that the fat content ranged from about 23 to 52 Gm. and protein from 102 to 190 Gm., and that about 90 per cent of both components was of animal origin. These foods supplied 100 to 180 mg. of cholesterol per day.

TABLE II

Approximate Composition of Diet No. 1

Subject	Protein	Fat	Carbohydrate	Cholesterol	Total calories	Calories supplied by fat
	Gm.	Gm.	Gm.	mg.		%
A	102	23.1	323	100	1908	10.9
B	189.5	45.2	449	180	2968	13.9
C	137	46.4	321	140	2249	18.9
D	164.5	51.7	398	150	2605	17.8
E	164.5	43.8	410	150	2674	14.8

Diet No. 2

This ration, designed to be low in fat and high in cholesterol, was obtained by adding three scrambled or boiled eggs calculated to provide about 800 mg. of cholesterol. The animal fat component was decreased by the amount of fat supplied by the eggs. This diet was eaten for a period of one week, the fifth of the experiment.

Diet No. 3

This ration, designed to be high in vegetable fat and low in cholesterol, was obtained by adding about 70 Gm. of fat in the form of peanut oil, corn oil, or margarine to Diet No. 1. The total caloric intake was maintained approximately constant by the reduction of carbohydrate, a change that was made spontaneously by the subjects. This diet was eaten for a period of one week, the sixth of the experimental period.

Diet No. 4

This ration, designed to be high in animal fat and to contain a moderate amount of cholesterol, was obtained by adding about 70 Gm. of animal fat, mainly in the form of lard, to Diet No. 1. The cholesterol intake was calculated to be about 210-300 mg. per day. This diet was eaten for a period of two

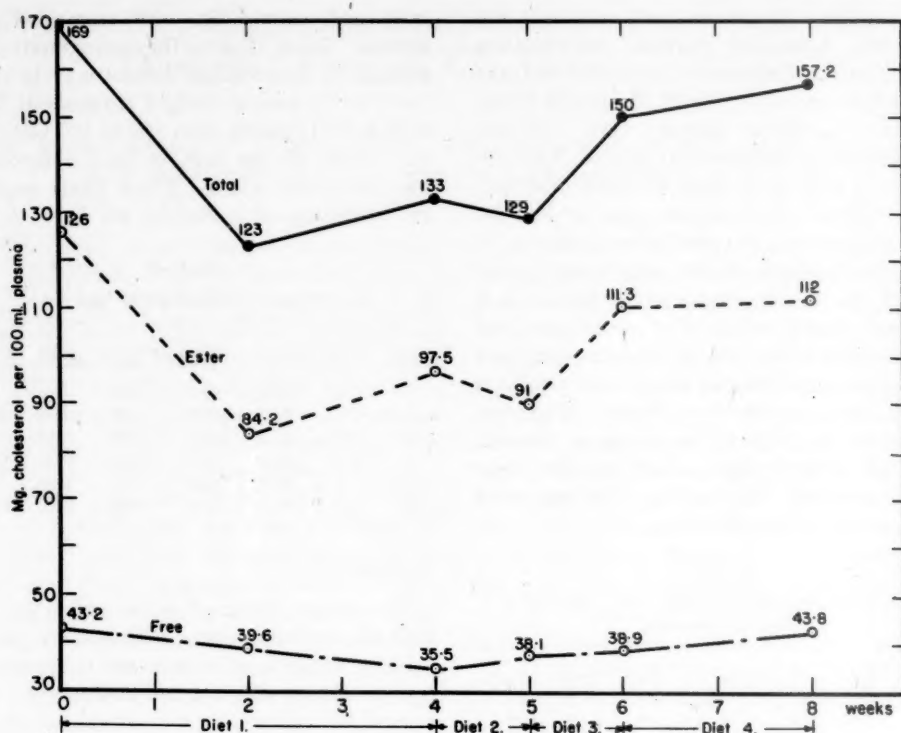


Fig. 1. Mean cholesterol levels of the five subjects throughout the experimental period.

weeks, the seventh and eighth of the experimental period.

RESULTS

Figure 1 shows the mean cholesterol levels during the entire experimental period. The individual data on the five subjects are presented in Table III. A statistical analysis of the results was performed by the procedure outlined by Bernstein and Weatherall,¹⁸ in which the significance of the mean of the differences was tested (see Table IV).

DISCUSSION

The change from a normal mixed hospital diet, which supplied 33–50 per cent of the total calories in the form of fat and between 300 and 1000 mg. of cholesterol per day, to a diet in which fat provided only 11–19 per cent of the total calories and between 100 and 180 mg. of cholesterol led to a rapid and significant decrease in both esterified and free cholesterol

(respectively $P = < 0.01$ and 0.02), by far the greater change occurring in the former fraction. It may be noted that in the case of Subject D, despite the fact that his diet provided 18 per cent of the calories in the form of fat, a figure at the upper range of the group values, his cholesterol level decreased from 141 to 83 mg. per 100 ml. plasma. It would appear, therefore, that it is not necessary to subject patients to an extreme restriction of fat in order to effect a significant decrease in plasma cholesterol. Keys¹⁰ noted a lowering of only about 20 per cent when subjects were shifted from a standard diet providing 150 Gm. of fat and 600 to 700 mg. cholesterol per day to a diet devoid of cholesterol and supplying only 15 Gm. fat per day. This response, while qualitatively the same as that noted in our work, is quantitatively different, being much smaller than that noted by us. In this connection, it is of interest that the decreases from individual to individual could not be re-

TABLE III
Plasma Cholesterol Levels of Five Subjects Ingesting Diets Differing in Fat and Cholesterol Content.
Individual Data

Subject	Age (years)	Weeks	Diet	Wt. in lb.	Total cholesterol*	Cholesterol*	
						Free	Esterified
A	39	Start	1	186	223.0	63.6	159.4
		2	1	188	186.0	56.1	129.9
		4	1	186	186.5	49.5	137.0
		5	2	183	174.5	51.0	123.5
		6	3	185	193.0	48.7	144.2
		8	4	189	182.0	53.5	122.5
B	33	Start	1	157	167.0	43.4	123.6
		2	1	156	124.5	40.4	84.1
		4	1	156	119.0	32.7	86.3
		5	2	154	127.0	36.8	90.2
		6	3	155	137.0	37.5	99.5
		8	4	157	140.0	41.5	98.5
C	24	Start	1	156	172.0	44.6	127.4
		2	1	156	144.0	42.0	102.0
		4	1	153	144.0	36.2	107.8
		5	2	152	148.0	40.6	107.4
		6	3	153	169.0	42.0	127.0
		8	4	154	173.0	47.9	125.1
D	24	Start	1	164	140.5	31.7	108.8
		2	1	161	83.3	30.9	52.4
		4	1	163	97.0	27.8	66.2
		5	2	157	89.0	30.6	58.4
		6	3	158	130.0	35.0	95.0
		8	4	157	134.0	38.8	95.2
E	23	Start	1	183	146.0	33.1	112.9
		2	1	184	81.0	28.5	52.5
		4	1	184	122.0	31.5	90.5
		5	2	181	107.0	31.7	75.3
		6	3	183	122.0	31.3	90.7
		8	4	180	156.5	37.5	119.0

* Total, free, and esterified cholesterol expressed in terms of mg./100 ml. plasma.

TABLE IV
Comparison of the Significance of the Mean of the Difference in Plasma Cholesterol Levels on Different Dietary Regimes

Comparison between values obtained on following diets	Total cholesterol		Free cholesterol		Ester cholesterol	
	Change in mg./100 ml.	Probability	Change in mg./100 ml.	Probability	Change in mg./100 ml.	Probability
Pre-test vs. Diet 1 at end of 2 weeks	-46.2	< 0.01	-3.7	0.02-0.05	-42.2	< 0.01
Pre-test vs. Diet 1 at end of 4 weeks	-36.5	< 0.01	-7.7	0.02	-28.8	< 0.01
Pre-test vs. Diet 2	-41.0	< 0.01	-5.1	0.05-0.1	-37.4	< 0.01
Pre-test vs. Diet 3	-19.8	≈ 0.02	-4.4	0.2-0.3	-15.2	≈ 0.02
Pre-test vs. Diet 4	-12.7	0.2-0.3	+0.6	0.9	-13.9	0.1-0.2
Diet 1 vs. 2	-3.4	0.5	+2.4	≈ 0.05	-4.6	≈ 0.2
Diet 1 vs. 3	+17.0	0.02-0.05	+3.3	≈ 0.1	+13.7	≈ 0.05
Diet 1 vs. 4	+24.0	0.02-0.05	+8.3	< 0.01	+14.5	0.1-0.2

lated closely to the fat intake. For example, Subject A, whose diet provided 10.9 per cent of the total calories in the form of fat, exhibited a decrease of 37 mg. or 16.6 per cent, whereas Subject D, whose diet supplied 17.8 per cent of the caloric intake in the form of fat, showed a decrease of 57 mg. or 40.6 per cent. It may therefore be concluded that widely varying degrees of fat restriction can produce similar decreases in plasma cholesterol levels. For this reason, any prescription of diets designed to lower blood cholesterol should be controlled by determinations of this lipid, and the least troublesome dietary modification that produces the desired decrease should be prescribed. A similar conclusion has also been reached by Hildreth *et al.*¹¹

Both Keys¹⁰ and Mellinkoff, Machella, and Reinhold¹⁹ have reported that when dietary alterations are made that affect cholesterol levels, the major change occurs during the first week to 10 days. An examination of the data in Table III provides some confirmation of this statement, inasmuch as the greatest alteration was noted after an interval of two weeks on Diet 1.

Despite the fact that approximately 800 mg. cholesterol per day were taken in the form of egg yolk in the subsequent period, no demonstrable change was observed in plasma cholesterol levels. This agrees with the findings of Keys *et al.*⁵ and Hildreth *et al.*,¹¹ but is in conflict with those of Messinger *et al.*⁷ However, the proper interpretation of the latter work is made difficult by the fact that no attempt was made by these investigators to control the level of dietary fat. The addition of 150 Gm. of egg yolk powder would add approximately 95 Gm. of fat per day to the diet, and the effect of animal fat in increasing plasma cholesterol levels appears to be fairly well substantiated, as indicated below. Furthermore, the latter workers utilized about five times as much egg yolk as was eaten by the subjects in our study, and this may explain the wide difference in the results obtained.

The addition of 70 Gm. per day of vegetable fats to Diet 1 led to a significant increase in plasma cholesterol. This finding is in agree-

ment with that of Hildreth *et al.*¹¹ and Keys *et al.*,⁵ and emphasizes once more the importance of the level of dietary fat, no matter what the source. However, both Groen *et al.*¹⁴ and Kinsell *et al.*^{12,20} present rather convincing evidence that the change from a diet containing animal fat to one containing vegetable fat is associated with a significant decline in plasma cholesterol values. Additional information supporting this view has been recently published by Hardinge and Stare²¹ who found that "pure" vegetarians exhibited lower serum cholesterol levels despite a free intake of vegetable fat. These conflicting conclusions indicate the necessity for further work in this field in order to elucidate the role of dietary fats in affecting plasma cholesterol levels.

The substitution of animal fat for the vegetable fat resulted in a further but insignificant increase in plasma cholesterol to levels that almost undoubtedly would have been reached had the diet high in vegetable fat been continued for a similar length of time. Under the conditions used here, therefore, no distinction could be made between vegetable and animal fat in effecting an elevation of plasma cholesterol.

SUMMARY

Five apparently healthy male subjects were placed upon diets having the following characteristics:

- (1) 100 to 180 mg. cholesterol per day and 10.9 to 18.9 per cent of the total calories in the form of fat.
- (2) 900 to 980 mg. cholesterol daily and with the same proportions for fat.
- (3) 100 to 180 mg. cholesterol per day and 34 to 46 per cent of the total calories in the form of vegetable fat.
- (4) 210 to 300 mg. cholesterol per day and 34 to 46 per cent of the total calories in the form of animal fat.

The diet low in fat and in cholesterol led to a highly significant decrease in plasma cholesterol levels, whereas the addition of cholesterol in the form of egg yolk did not cause any change. When the proportion of dietary fat was increased in the form of vege-

table fat, a significant increase occurred in plasma cholesterol levels, and these values were not further significantly increased by a substitution of animal fat for the vegetable fat. The results of this investigation indicate that, within the limits used here, dietary cholesterol has no effect on plasma cholesterol levels, whereas alterations in the level of dietary fat, whether of animal or vegetable origin, led to parallel changes in plasma cholesterol.

ACKNOWLEDGMENTS

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RESUMEN

Dieta y niveles plasmáticos de colesterol

Cinco sujetos de sexo masculino gozando, según las apariencias, de buena salud, fueron sometidos a dietas con las siguientes características:

(1) 100 a 180 mg. colesterol/día y 10,9 a 18,9 por 100 de las calorías totales en forma de grasas.

(2) 900 a 980 mg. colesterol/día y con las mismas proporciones de grasas.

(3) 100 a 180 mg. colesterol/día y 34 a 46 por 100 de las calorías totales en forma de grasa vegetal.

(4) 210 a 300 mg. colesterol/día y 34 a 46 por 100 de las calorías totales en forma de grasa animal.

La dieta pobre en grasas y en colesterol indujo un descenso muy significativo de los niveles plasmáticos de colesterol, mientras que la adición de colesterol en forma de yema de huevo no causó ningún cambio. Cuando la proporción de grasa dietética fué aumentado

por la adición de grasa vegetal, hubo un aumento significativo de los niveles plasmáticos de colesterol, y estos valores no fueron significativamente aumentados por la sustitución por grasa animal de la grasa vegetal. Los resultados de esta investigación indican que, dentro de los límites observados aquí, el colesterol dietético no afecta en nada los niveles plasmáticos de colesterol, mientras que cambios en el nivel de grasa dietética, sea ésta de origen animal o vegetal, resultan en cambios paralelos del colesterol plasmático.

Scurvy in Adult Africans

A Clinical, Haematological, and Pathological Study

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ALL THE OLDER reports^{1 6} on scurvy in the South African Bantu (Africans) have dealt with the appearance of this disease either in abnormal times or amongst selected communities such as mine labourers. The present communication is concerned with scurvy amongst urbanised Africans living side by side with a white community. In these people the disease is viewed against a background of chronic malnutrition and presents some unusual features not previously described.

MATERIAL, METHODS AND CRITERIA FOR DIAGNOSIS

Twenty-nine males and one female between the ages of 30 and 60 were studied. All except the woman, a housewife, were general labourers; seven were builders' hands. Their diet consisted mainly of maize porridge, bread, and small quantities of meat and cooked vegetables. The only sources of vitamin C in such a diet are the meat and vegetables which the Africans cook for long periods. Compared with the patients, a control group of 100 nonscorbutics claimed to eat less porridge but more meat and vegetables.

For the first 3-7 days while preliminary studies were made, they received no specific treatment unless their clinical condition warranted it; thereafter 29 patients received 1000 mg. of ascorbic acid intravenously followed by 500 mg. intramuscularly or orally every day for the duration of their stay in hospital. Twenty patients were allowed a full ward diet containing about 75 mg. of ascorbic acid daily, nine were restricted to food simulating their

home diet, and one was kept on "home" diet without ascorbic acid for two weeks.

In the majority of patients the diagnosis of acute scurvy was confirmed by biopsy evidence of recent spontaneous haemorrhage into muscle, subcutaneous tissue, or skin which responded rapidly to the administration of vitamin C.

Incidence

Forty scorbutics comprising 0.13 per cent of all hospital admissions were seen from August 1952 to July 1953, but the incidence of the disease was probably higher, as mild cases were not admitted. In common with other reports from South Africa, the disease appeared mainly in spring and summer and was seen only twice in females and once in an infant.⁷

CLINICAL FEATURES, AND THE COURSE OF THE TREATED DISEASE

None of the patients gave a history of diarrhoea, vomiting, or other obvious precipitating factor, and some, whose conditions of diet and work had been unchanged for years, inexplicably developed scurvy. Twenty patients complained of symptoms for 1-4 weeks, seven for 2-3 months, and three for 2-3 years.

In every patient haemorrhage was found in the muscles of the lower limbs, and in only one case were the forearm muscles affected as well. In consequence the physical signs predominated in the legs; pain in these sites was the most common complaint. Twenty-four patients showed evidence of a general bleeding tendency and/or hypertrophic gums, but in five, isolated haemorrhage in the leg muscles was the main sign of the disease (Table I).

From the Baragwanath Hospital and University of Witwatersrand.

TABLE I
Incidence of Clinical Signs in 30 Scurbutics

	No. of Cases
Muscle haemorrhage, general bleeding, and hypertrophic gums	14
Muscle haemorrhage and general bleeding	2
Muscle haemorrhage and hypertrophic gums	8
Muscle haemorrhage alone (Hb. 10.0, 11.7, 14.3, 15.1, 16.4 Gm. per 100 ml.)	5
Hypertrophic gums alone	1
TOTAL	30

General State

Most patients were spare, a few were fat and flabby, and none was emaciated. About half were febrile; the temperature ranged from 99 to 102° F. and the pulse rate was raised proportionately. Fifteen patients were very ill on admission; they were apathetic and breathless on the slightest exertion. Most of these were anaemic (Hb. 6–10.5 Gm. per 100 ml.) or had high temperatures. Eight patients were quite well and the remaining seven, though not apparently ill on admission, showed striking improvement in their general condition on treatment. With treatment, elevated temperatures returned to normal in 2–8 days. Even very ill patients were ambulant in 2–3 weeks, but patients who had been severely anaemic improved much more slowly, their apathy persisting for about a month. The type of diet did not appear to influence the course of the disease.

In four patients an alarming collapse occurred during their first week in the hospital. They suddenly became cold and mentally confused, developed thready pulses, and looked very ill. All had been anaemic on admission (Hb. range 6.5–10.4 Gm. per 100 ml., Cases 1, 6, 10, 15, Table II), and only one had been receiving ascorbic acid. In three the incident took place after posing for photography or x-ray examination, but the fourth collapsed in bed for no apparent reason. In three the haemoglobin level after the collapse was considerably lower than it had been 24–48 hours previously (range 1.4–3.4 Gm. per 100 ml.), but no evidence of fresh external or internal bleeding was found. Only two were treated

during the attack with intravenous ascorbic acid, but all four recovered within 3–4 hours.

One patient suddenly collapsed and died 24 hours after admission before ascorbic acid had been administered. He had a large haemorrhage into the muscles of one leg, and he was anaemic (Hb. 7.9 Gm. per 100 ml.), but did not look seriously ill.

The Lower Limbs

Both legs were affected in twenty patients, but in ten the lesion was unilateral. Almost invariably the haemorrhage was found in the calf, the posterior aspect of the thigh, the popliteal region, or the tissues around the ankle. Usually the lesion was localised and well defined. A strip on the lateral aspect of the calf was commonly affected (Fig. 1). The overlying skin was darkly stained or oedematous and brawny; the lesion felt hot and dry and formed a hard tender mass. In

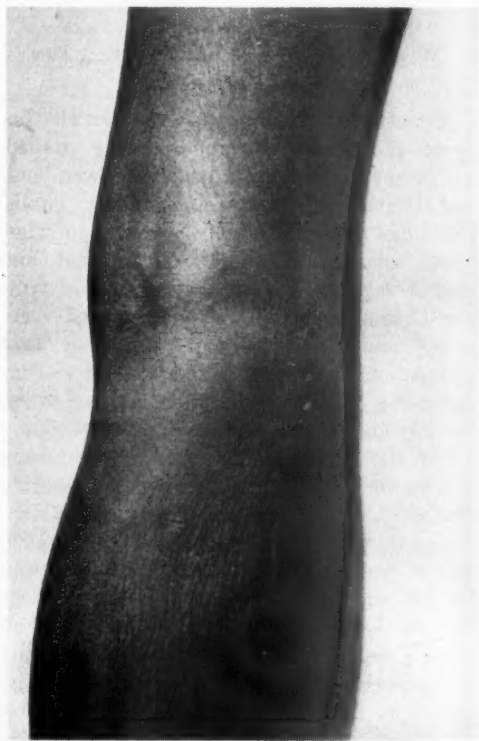


Fig. 1. Haemorrhage in the lateral calf muscles. The skin is stained and "oedematous."



Fig. 2. Scarring and pigmentation of the sock area 2 months after an acute attack of scurvy.

ten patients the haemorrhage was more generalised, affecting the whole calf or the entire limb from the level of the mid-thigh.

Chronic Changes

Although in the majority of cases the extravasated blood became absorbed in 4 to 6 weeks, leaving no scar, in some patients chronic tissue changes developed. These were seen most commonly round the ankle and less frequently in the calf. Of nine patients with haemorrhage around the tissues of the ankle the pigmentation persisted in four; the skin and subcutaneous tissues became tightly bound down and movement at the joint was restricted; the natural markings were obscured and the ankle and foot took on a cadaveric appearance. These pigmented socklike areas of adherent skin remained as stigmata which could be recognized as long as 6 months later (Fig. 2). Similar changes extending to the calf developed in a patient with massive haemorrhage affecting both calves and thighs. After 16 weeks of ascorbic acid therapy his thighs had recovered but both calves remained hard, the skin and deeper tissues being inextricably bound together.

In two patients with acute haemorrhage into one leg the opposite limb was abnormal (Figs. 3 and 4). From knee to foot this leg was thin and covered by smooth hairless skin; the calf felt hard and woody, was not hot or tender, and the skin was tightly bound to the deeper structures, producing a picture reminiscent of localised scleroderma. Movement at the ankle joint was restricted to 5° of flexion and extension. Both patients gave similar histories. They claimed that 2-3 years previously the thin leg had been painful and swollen, as the acutely affected leg was now, and that it had become tight and stiff over the ensuing months. Their gums had bled spontaneously or after brushing their teeth ever since the original illness, which had not been treated. After 6 weeks of ascorbic acid therapy the acute extravasations resolved and their gums improved. After a further 6 months of treatment the tightness around the ankle of the thin leg became less marked and movement at the joint was freer.

General Bleeding Tendency

Of these thirty patients only 16 showed clinical evidence of a general bleeding tendency, namely, one or more of the following signs: perifollicular purpura, ecchymoses, subungual haemorrhages, haemarthroses, or superficial haematomata.

Gums

Nineteen patients showed the well-known gum lesions of scurvy while seven had normal teeth and gums. In the remaining four patients the gums were not typically hypertrophic but appeared septic and improved considerably after treatment. One patient (Case 17, Table II) had fungating gums for which no etiology could be found. He was moderately anaemic (Hb. 10.5 Gm. per 100 ml.) but had no extravasation of blood in his limbs or evidence of generalised bleeding. The gums and the anaemia both responded to ascorbic acid therapy. It seems likely that he was the type of scorbutic who presents with only gum lesions as described by Fox.⁶

The *spleen* was moderately enlarged in four patients and in two of these the splenomegaly



Fig. 3. Chronic scurvy; the left leg is thin and tight.

appeared two weeks after admission and persisted for three months.

None of the thirty patients studied was aware of having bled from the bowel or the kidney, and apart from three who had positive benzidine tests such bleeding was not found in the rest despite regular urine and stool examinations. One patient had repeated epistaxes. During the period of this study no signs of scurvy were found in a control group of twenty patients with bloody effusions (pericardial, pleural, peritoneal), five with haematemesis, several with epistaxis and haematuria.

Oedema

In several patients with extensive lesions of the legs the swelling became less after merely a few days of bed rest, and it was assumed that the swelling was partly due to oedema. Moreover, five patients with unilateral leg lesions had oedema of the ankle which disappeared as the extravasation in the muscles resolved. Twelve patients, however, whether they had unilateral or bilateral leg



Fig. 4. The same leg in side view showing involvement of the calf. The hair follicles are hyperkeratotic.

lesions, exhibited mild pitting oedema of both ankles and, moreover, three had sacral oedema as well. In most of these, post-exertional oedema of the ankles persisted for a few weeks after recovery from the acute attack, but in five cases it was still evident 6 months later. In ten oedematous patients, weights and 24-hour urinary outputs were studied. Whether treated or not, they all lost 3-7 lb. in the first week and regained their previous weight in the following 10 days. Ascorbic acid did not provoke an obvious diuresis. The oedema did not appear to be of cardiac or renal origin. The majority of these patients were anaemic on admission, but ankle oedema still appeared after exercise weeks or months after their haemoglobin had returned to normal.

TABLE II
Serial Haemoglobin Values in Treated Scorbutics (Gm. per 100 ml.)

Case No.	Days														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	6.5	6.5	7.3	5.9	6.4			8.3				9.8			10.5
2	7.2						7.8						9.1		
3	7.8		7.1			8.5	8.5		9.8			11.1		11.1	
4	7.9				8.9			10.5				10.3			
5	7.9							12.7		9.5				10.9	
6	7.9			8.2	9.8	9.4							12.2		
7	8.0	8.2					11.6		11.0				11.6		14.4
8	8.3			8.6		12.6		8.9		10.1	10.3		10.7		11.5
9	8.8			9.1				9.7			11.2			10.7	
10	9.2		10.6	7.9	6.6	8.6		10.1		10.6		12.3	12.8		
11	9.2						11.2				12.2			11.4	12.8
12	9.8			7.8				9.1		9.3					11.4
13	10.0		7.2		10.6		11.8		9.2					15.3	
14	10.3		9.5		9.5		9.5					11.6			
15	10.4				12.7	9.3	9.1	9.1				9.3	10.5		
16	10.5														13.0
17	10.5			11.8			11.4		11.7						
18	10.6				13.2		11.5				13.5		13.1		
19	11.0					9.5		11.6							
20	11.2				11.6		11.0				12.3		12.3	12.8	
21	11.7								13.0						14.9
22	11.7														12.9
23	13.0					13.0		13.0		14.9					11.3
24	13.8			13.0				14.5	13.5						13.1
25	14.3														15.8
26	14.5						14.4								
27	15.1														
28	15.1														14.4
29	15.6						17.0								
30	16.4						17.8								

[illegible]

Jugular Venous Pressure

In 11 patients the level of deep jugular venous pulsation was raised in relation to the sternal angle;⁸ a positive hepato-jugular reflux could be elicited. The raised level of the venous pulse was associated with oedema in some cases and anaemia in others, but not consistently with either. As a rule it had disappeared within a month, but in two patients it persisted for 2 and 4 months, respectively, and in others it appeared for the first time in convalescence. There was no other evidence of heart failure and no cardiac enlargement was found radiologically. In routine x-ray examination of the chest, 9 of 22 cases showed marked dilatation of the main pulmonary artery.

Skin

In 14 patients the hair follicles were hyperkeratotic; in nine the papules on the legs, but not on the arms, appeared at the sites of previous perifollicular haemorrhages. One third of 100 nonscorbutic controls showed similar hyperkeratotic hair follicles. Although pellagra is a common disease in Africans, none of the thirty scorbutics showed the skin lesions of this disease or other vitamin B deficiencies.

Bones

In five of 15 patients x-rayed during the acute attack, periosteal roughening was seen over the tibia or fibula, and in one patient a small ridge of heterotopic bone had formed 3 months later. Both chronic cases showed osteoporosis, one of the bones around the ankle, the other of those around the knee. Two other patients had well-marked osteoporosis of the spine and collapse of several vertebrae.

LABORATORY INVESTIGATIONS

Blood and Marrow

All patients had full blood counts on admission and thereafter frequent haemoglobin estimations (oxyhaemoglobin and Klett photoelectric colorimeter). Twenty-two patients were anaemic on admission (Hb. 11.7 Gm. per 100 ml. or less), but eight were not

(Hb. 13 to 16.4 Gm. per 100 ml.) (Table II). In every instance the anaemia was normochromic and normocytic and was accompanied by leucopenia.

Although most patients with haemoglobin below 11.7 Gm. per 100 ml. had moderate or large extravasations in the limbs, in some cases there was a striking disparity between the severity of the anaemia and the extent of the tissue haemorrhage, e.g., one patient with a haematoma measuring 2 x 2 inches in the anterior thigh muscles had 7.9 Gm. per 100 ml. of haemoglobin.

The severe anaemias yielded rapidly to treatment. Patients with initial haemoglobin levels of under 11.0 Gm. per 100 ml. gained 3.8-6.6 Gm. per 100 ml. in 2-3 weeks. The precise rate of gain was obscured by wide fluctuations in the haemoglobin levels when these were estimated at frequent intervals. In six patients, at some stage in the disease the haemoglobin value suddenly fell by 2.0 Gm. per 100 ml. or more within 24-48 hours (Cases 5, 8, 10, 12, 13, 15, Table II). One patient apparently lost 4.0 Gm. per 100 ml. of haemoglobin in 48 hours (Case 10) and another 3.4 in 24 hours (Case 15). In three patients equally rapid rises of haemoglobin followed the falls (Cases 10, 13, 19). In five patients these losses of haemoglobin were associated with no change in the clinical state even when they were ambulant, but in three the lower haemoglobin values were found after they had collapsed. These variations in haemoglobin level were not due to fresh external or internal haemorrhage as far as could be determined. Since in three instances the falls of haemoglobin appeared to be related to exertion, the effects of a standard exercise were tested in eight scorbutics and three controls. A definite fall occurred in only two scorbutics (range 1.2-1.6 Gm. per 100 ml.), but in the rest there was no significant change.

Patients kept on a "home" diet and treated with ascorbic acid attained normal haemoglobin levels in approximately the same times as those who were on full ward diet, but the solitary patient maintained on home diet without ascorbic acid for two weeks showed no gain of haemoglobin and deteriorated clinically.

With haemoglobin values of 11.0 Gm. per 100 ml. or more on admission, reticulocyte counts were usually 2 per cent or less and no increase was observed with treatment. Of those patients with initial haemoglobin under 11.0 Gm. per 100 ml. half had 2.0 per cent reticulocytes on admission and the rest 4-8.8 per cent; most of these showed a marked response with treatment which in four cases reached 15 per cent. The *sternal marrow* examined in six patients showed a normoblastic hyperplasia in two and was normal in the remainder.

Blood Proteins

The blood protein concentrations of all patients, whether oedematous or not, were abnormal. As compared with a random group of 100 apparently healthy African labourers,⁹ the average total protein was low (av. 7.1 Gm. per 100 ml. as compared with 8.4) the albumen fraction reduced (av. 2.5 Gm. per 100 ml. as compared with 3.8), and the A/G ratio reversed; fibrinogen levels lay within normal limits. With clinical recovery there was a rise in the average level of the total proteins and the albumen fraction to 7.4 and 3.0 Gm. per 100 ml., respectively. It is worthy of note that the five patients who still developed ankle oedema months after their acute attack of scurvy also showed a rise in the level of their blood protein.

Liver Function Tests

Thymol turbidity, thymol flocculation, Ucko's modification of the Takata-Ara and the colloidal red test were usually abnormal, i.e., they deviated more from the normal than those of a random series of medical patients and did not change significantly after recovery. The alkaline phosphatase was normal throughout.

Other Studies

Bleeding times, coagulation times, and platelet counts were normal. In 16 patients the prothrombin index was 100 per cent, but in the remaining 14 it lay between 72 and 94 per cent and became normal within a week

of treatment. Capillary fragility tests (Hess' method¹⁰) were positive in only six patients and became negative within a week of treatment. The serum bilirubin, estimated in twenty patients, was raised in 11 to 2.4 mg. per 100 ml., and of these, five had an excess of urobilin in the urine. The erythrocyte sedimentation rate (Wintrobe) in ten patients examined was disproportionately raised even after correction for the anaemia. Vitamin C saturation tests¹¹ were done more to confirm unsaturation than as a diagnostic measure, since normal Africans have little or no reserve of the vitamin.⁶ Twenty patients and ten controls were found to be unsaturated.

Muscle Abscess

Abscesses in muscle occur in Africans occasionally, and during the period of this study five such cases were seen, four in the calf and one in the biceps. In three a suppurating haematoma was found at operation, but no organism was recovered. None of these patients gave a history of trauma or had associated evidence of scurvy, but four were anaemic (Hb. 10 Gm. per 100 ml. or less). On full ward diet all recovered after surgical drainage. These abscesses may have been examples of tropical pyomyositis,¹² but the sterile pus, the haematomata, and the anaemia seemed to point to scurvy as a possible basis for the condition. On the other hand, none of the 30 scorbutics studied ever developed abscesses even after biopsy, nor was a case of scurvy seen with haemorrhage in one leg and an abscess in the other.

PATHOLOGIC FINDINGS

Technique

Biopsies of the skin, subcutaneous tissue, and muscles were taken from ten controls and 27 scorbutics at various stages of the disease. Sections were stained with haematoxylin and eosin, and, where necessary, with van Gieson's stain for collagen and by Wilder's silver impregnation techniques for reticulin; the presence of haemosiderin was demonstrated by Perl's stain. Subsequent biopsies were taken about an inch away from the original wound.

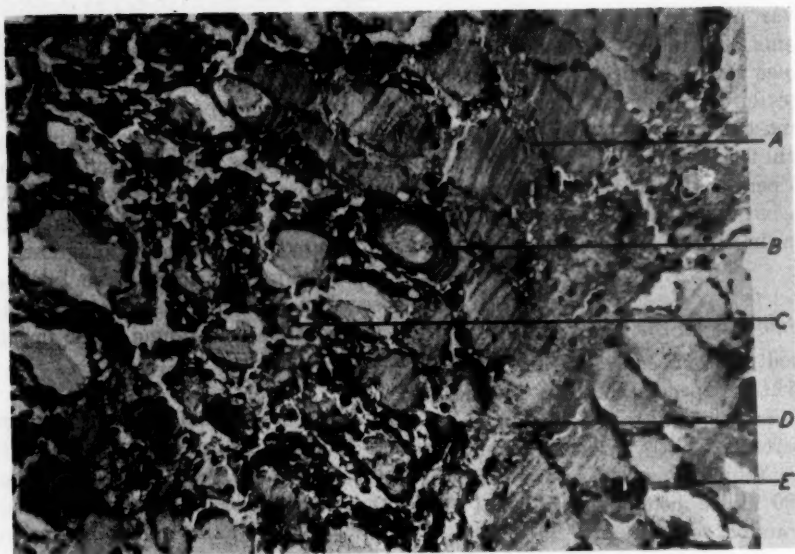


Fig. 5. Haematoxylin and eosin $\times 150$. Section of haemorrhagic muscle. A. Endomysial haemorrhage. B. Haemorrhage within sarcolemma. C. Degenerated muscle fibre. D. Perimysial haemorrhage. E. Hemosiderin pigment between muscle fibres.

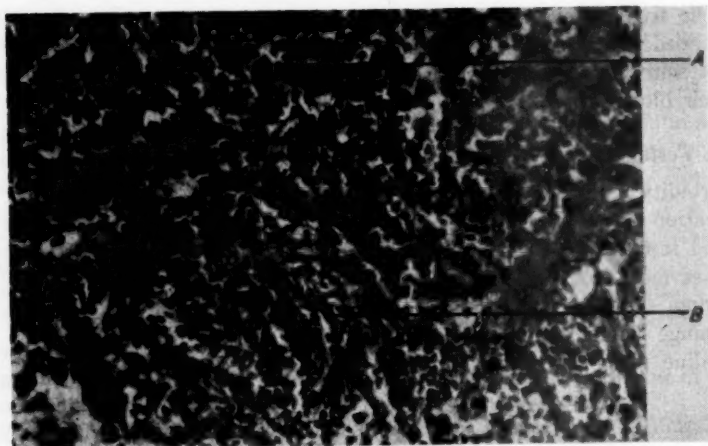


Fig. 6. Haematoxylin and eosin $\times 430$. Biopsy from muscle showing gross destruction. A. Fibres with non-specific staining reaction. B. Invading primitive fibroblast.

Findings

The controls showed no abnormality of skin, subcutaneous tissue, or muscle.

Acute Scurvy

Biopsies were performed on 25 patients in the acute attack before or within the first few days of treatment. Macroscopically, there was usually obvious haemorrhage in skin and subcutaneous tissue, and the deep fascia looked dull and lacked lustre; the muscle was firm, plum-coloured, and did not contract when pinched.

Microscopically, extravasation of red cells was most marked at the junction of dermis and subcutaneous tissue, and this area was always affected even when bleeding was minimal. Varying degrees of haemorrhage were present in the adjoining subcutaneous tissue and dermis. The haemorrhagic areas showed commencing organisation similar to that observed in experimental scurvy in guinea-pigs.^{13,14} This consisted of invasion by numerous large immature fibroblasts, newly formed capillaries and haemosiderin-laden phagocytes. Unlike the findings in completely scorbutic guinea-pigs, irregular reticulin formation was observed. In addition, many cases showed abnormal argyrophilia of fibrils within mature collagen fibres throughout the dermis. No collagen formation, however, could be demonstrated in the haemorrhagic areas.

Histologic Changes in Muscle

All acute cases showed haemorrhage in the muscle which was often patchy in distribution. In seven cases haemorrhage was seen in the peri- and endomysial connective tissue planes and occasionally within the sarcolemma, but the tissue was clearly recognisable as muscle. In 18 cases the muscle fibres had been entirely replaced by haemorrhagic tissue undergoing organisation; in these areas only remnants of the characteristic reticulin framework of striated muscle and a few necrotic fragments of muscle were present. These areas of gross muscle destruction were sometimes found lying adjacent to apparently normal fibres. Sec-

tions from unaffected muscles, 3 pectorals and 2 gastrocnemii, showed no abnormality.

Histologic Findings after Clinical Recovery

In eight patients who showed clinical resolution of their lesion, a second section was taken at intervals of 2 weeks to 6 months after the first biopsy. These sections revealed little besides haemosiderin-laden phagocytes in the perivascular connective tissue, around the dermal appendages, and in the peri- and endomysium; in two patients there was, in addition, a slight increase in the collagen fibres of the perimysium.

Chronic Changes

Biopsies from the ankle and calf were taken from four patients showing chronic changes clinically, i.e., tight legs and/or ankles. Skin and subcutaneous tissue were inseparably bound together, forming a thick hard rind, and the edges of the biopsy wound stood up rigidly and felt gritty; the muscle looked normal and contracted readily on stimulation. Microscopically, dense collagen fibres had wholly or partly replaced the subcutaneous fat and merged with the dermis. There was much haemosiderin pigment around the vessels and dermal appendages. The muscle showed no fibrosis or other abnormality apart from blood pigment in the sites already described.

Autopsy Findings*

In the patient who died, the calf showed large strips of haemorrhage into muscle and subcutaneous tissue; a few ecchymoses were found in the muscles of the other leg. Numerous petechial haemorrhages were present over the surfaces of the heart, lungs, and peritoneum. The pleural and pericardial cavities contained 1-2 ounces of blood-stained effusion. The liver, spleen, and duodenum showed severe haemosiderosis. There was no evidence of haemorrhage elsewhere, nor was the immediate cause of death apparent. Microscopic examination of the haemorrhagic tissues revealed changes similar to those described above. The liver showed a moderate increase of periportal fibrous tissue.

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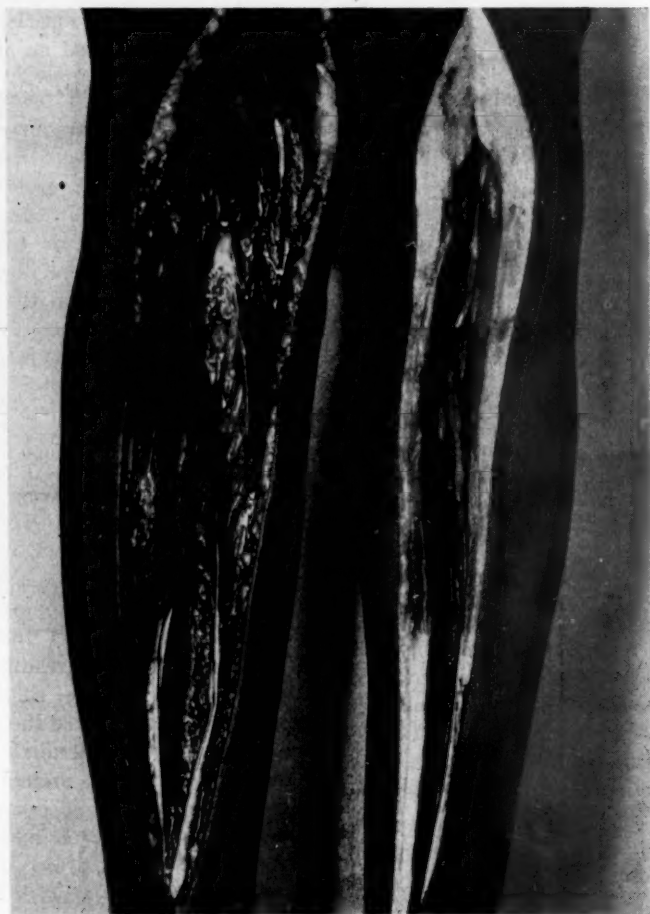


Fig. 7. Post-mortem section of the affected leg showing large strips of haemorrhage lying in the calf muscles.

DISCUSSION

In most respects, scurvy in Africans follows the well-known course described in other races. The disease appeared more frequently in spring and summer when fruit and green vegetables were plentiful and cheap. Again, it was rarely found in children or in females, although there were no striking differences between the diets of women and men nor between scorbutics and nonscorbutics. These paradoxes have been regarded by others as evidence of individual variation in absorption and utilisation of vitamin C.¹⁵ The four patients who collapsed and the one who died were all anaemic,

but neither the clinical observations nor the autopsy gave any clue to the etiology of these well-known hazards of the disease.

Certain of our other findings appear to be unusual and to merit discussion. As far as we are aware, no mention is made in the literature, either in experimental animals or in man, of the extensive chronic changes described here. The two patients with thin, tight legs had almost certainly suffered from scurvy 2-3 years previously, and similar changes developed in hospital in a patient with massive haemorrhage in the leg muscles. From the histology it is clear that these changes in the

calf were merely an extension of the scarring which developed around the ankle in acute cases. These two chronic cases indicated, moreover, that scurvy might persist for years in a clinically detectable and active form, and that the chronic changes in the legs were still to some extent amenable to ascorbic acid therapy.

X-rays of the legs were taken in 15 of the 30 patients, but the spines were examined in only four who complained of backache. The two chronic cases showed osteoporosis of the bones around the ankle and knee joints; two others showed osteoporosis and collapse of several vertebrae. In experimental animals and in children it is known that osteoporosis of bones is one of the cardinal features of the disease. The question arises whether scurvy may not be responsible for unexplained cases of osteoporosis in Africans; this cannot be answered without further study.

None of the patients in this series had haemorrhagic effusions or gross bleeding from the bowel or kidney, but such incidents are described by others. The fact that six of these scorbutics presented with isolated haemorrhage in muscles or gums raises the question whether scurvy is responsible for the occasional case of unexplained haemopericardium, haemothorax, or haematemesis found at post-mortem in Africans. The clinical difficulties of proving that scurvy is responsible for such isolated bleeding are exemplified in patients with muscle abscesses in whom the response of the anaemia may have been entirely attributable to the surgical drainage of the pus. In the absence of associated signs of scurvy, similar problems attend the diagnosis of unexplained haemorrhagic effusions or bleeding seen in other patients.

When striking falls in the haemoglobin level were first encountered, it was thought that they might have been due to fresh internal or external haemorrhage. Measurements of the limbs and repeated stool, urine, and clinical examinations, however, failed to reveal evidence of fresh bleeding. Usually there was no increased bilirubinaemia, reticulocytosis, or change in the clinical picture to suggest intravascular haemolysis. Assumption of the erect

posture,¹⁶ which is known to produce a fall in the haemoglobin level, may have been responsible for some of the variations seen, but fluctuations in haemoglobin levels were observed in at least three patients who were confined to bed for weeks. Moreover, in three patients rapid gains followed the drop, and in view of these observations it seems likely that the haemoglobin fluctuations were due to variations in blood volume.

Oedema is mentioned in older descriptions of scurvy when it was encountered in moribund patients who were severely anaemic and had secondary infection of the bones.¹⁷ The oedema in this series appeared in patients during the acute attack, and since it affected not only the feet but the sacral pad as well, it could not have been due to distortion of tissues by blood. It could not be related to heart failure, renal disease, fatty diarrhoea or anaemia. The two factors which might be held responsible were the hypoalbuminaemia and the probable liver disease. However, in some patients, oedema persisted after the level of blood albumen had risen, and in others it disappeared despite the persistence of abnormal liver function tests.

Studies on undernourished subjects at Wuppertal¹⁸ showed that their oedema was increased by exercise and reduced by rest in bed; in some, the oedema persisted for months after taking a full diet. Moreover, in 20 patients investigated by cardiac catheterisation, half were found to have a raised right auricular pressure without other evidence of heart failure.¹⁹ McCance¹⁸ considered that the basic defect in these undernourished subjects was an increase in the volume of extracellular fluid which might affect the blood volume. In his opinion, the low level of blood proteins, by increasing the tendency to form extracellular fluid, aggravated the condition but was not primarily responsible for the oedema. These scorbutics, unlike McCance's subjects, probably suffered from liver disease, as many Africans do even when they appear to be healthy.²⁰ Whatever the primary etiology of the oedema in these scorbutics may be, it seems probable that a mechanism such as that described by McCance was responsible for the

oedema, the raised jugular venous pressure, and the fluctuations in the haemoglobin level.

SUMMARY

Thirty cases of scurvy in adult Africans were studied in the space of a year.

The disease commonly presented as an affection of the legs together with evidence of general bleeding and/or hypertrophic gums. Six cases, however, presented with isolated haemorrhage into muscle or gums. It is suggested that (in Africans) scurvy may be responsible for some cases of isolated haemorrhage from bowel, kidney, or serous cavities.

In two patients, extensive chronic changes were encountered in a leg which had been the seat of acute scurvy 2-3 years previously. Similar, less extensive changes developed during the acute attack in other patients.

The histopathology of tissues at various stages is described, and autopsy findings in one case are reported. Some patients showed osteoporosis of bones. Blood proteins and liver function tests were abnormal in all patients. Some patients showed generalised oedema; others showed elevated jugular venous pressure and fluctuations of haemoglobin level during the acute attack. It is suggested that these may be signs of variations in blood volume.

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We wish to express our gratitude to Dr. M. M. Suzman for his helpful criticism of the manuscript; to Dr. R. Cassel for numerous laboratory investigations; to Mr. H. D. Barnes for the vitamin C estimations of the urine; to Dr. A. G. Oettle for his opinion on the sections; to Drs. A. D. Bensusan and S. Wayburne for the photographs. The expenses of this investigation were partly defrayed by Merck and Co., Inc., Rahway, N. Y., U.S.A.

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RESUMEN

Escorbuto en Africanos adultos. Estudio clínico, hematológico y patológico

Treinte casos de escorbuto en Africanos adultos fueron estudiados durante el curso de un año.

La enfermedad se presentó por lo común como una afección de las piernas asociada con evidencia de hemorragia general con o sin encías hipertróficas. Seis casos, sin embargo, se presentaron con hemorragia aislada en los músculos o encías. Se sugiere que (en Africanos) el escorbuto es tal vez responsable de algunos casos de hemorragia aislada del intestino, del riñón, o de las cavidades serosas.

En dos pacientes, extensas alteraciones

crónicas se encontraron en una pierna que ya había sido el sitio de un escorbuto agudo hace dos o tres años. Cambios similares pero menores aparecieron en otros pacientes durante la fase aguda.

Se describe la histopatología de los tejidos a varias etapas de la enfermedad, y se presentan los hallazgos de autopsia en uno de los casos referidos. Algunos pacientes mostraron osteoporosis de los huesos. Las proteínas

sanguíneas eran anormales en todos los pacientes, y anormales también resultaron los tests de función hepática. En algunos pacientes había edema general; en otros, una elevada tensión yugular venosa y fluctuaciones del nivel de hemoglobina ocurrieron durante el acceso agudo.

Se sugiere que dichos fenómenos pueden constituir signos de variaciones del volumen sanguíneo.

The Use of Orally-fed Liquid Formulas in Metabolic Studies

By EDWARD H. AHRENS, JR., M.D.,* VINCENT P. DOLE, M.D.,† AND DAVID H. BLANKENHORN, M.D.‡

THE PERFORMANCE of exact metabolic studies in human subjects frequently is complicated by problems arising from the use of assorted natural foods. Strict adherence to dietary prescriptions demands elaborate calculations by dietitians and considerable reliance on the average values published in standard food tables. In order to achieve better definition of intake and to minimize analyses of dummy diets, many workers have resorted to the feeding of the same menu every day, or to the use of two- or three-day alternate menus. Kinsell and co-workers¹ have solved many of the problems inherent in the use of natural foodstuffs by preparing formula diets stabilized with Tween 80®. Designed for certain specialized metabolic studies, these formulas represented unusual proportions of fat, protein, and carbohydrate, and were for the most part administered through a polyethylene tube kept for weeks at a time in the stomach or duodenum. In the nutritional management of surgical patients, Barron² has tube-fed a regular hospital diet ground into a watery suspension in a colloid mill. Other workers³⁻¹⁰ have used orally administered fat emulsions as defined sources of fat in metabolic studies.

On the premise that balanced liquid formulas fed by mouth would be acceptable to adult

subjects for prolonged periods, we have compounded a number of mixtures and put them to trial during the past year. The present report is based on experiences with 30 adult patients given oral formula feedings as their sole nutriment for periods of 2 to 16 weeks. The formulas proved entirely acceptable, economical, and simple to use.

INGREDIENTS

Three basic formulas are given in Table I. These, with minor variations, have met the needs of four different types of metabolic study: (1) Variation in the amount of formula fed determined the caloric intake of obese subjects, without disturbing the composition of their diets. (2) Caloric levels remained constant while the proportions of protein, carbohydrate, and fat were varied. (3) Both the caloric value and the relative proportions of protein, fat, and carbohydrate were fixed in studies of a qualitative variable—the substitution of one type of fat for another. (4) Formula feedings have been used as a simple and effective means of limiting dietary sodium in the study of patients with hypertension, and of dietary copper in the study of patients with Wilson's disease.

The more elaborate experiments, such as the comparison of different dietary fats, show best the advantages of formula feeding. In these experiments protein was supplied by Lesofac®,* a commercial milk product very low

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* Lesofac (Wyeth), manufacturer's analysis as follows: Protein 50.0%, carbohydrate 39.2%, fat 1.0%, cholesterol 25 mg. %, ash 5.8% (including sodium 0.02, calcium 0.80, potassium 0.85, magnesium 0.10), moisture 4.0%, vitamin B₁ 2 mg. %, vitamin B₂ 4 mg. %, niacinamide 20 mg. %.

in fat and sodium. Carbohydrate, above the amount included in Lesofac®, was added as dextrose. Fat in the different formulas was provided by cream or butter fat, egg yolk, prime steam lard, corn oil, cottonseed oil, coconut oil, cocoa bean oil, or synthetic triolein. Some of these formulas were analyzed

control of fat or sodium and forms exceptionally smooth and durable emulsions. Ideally, one would like to have a single, defined protein, which is both nutritionally complete and free from accessory foods. Purified casein was used in trial emulsions, but proved a failure because the heavy denatured granules

TABLE I

Basic Formulas

Quantities given make one unit of 500 calories as calculated from the conventional values: protein and carbohydrate = 4 cal./Gm.; fat = 9 cal./Gm.

	Weight (Gm.)	P (Gm.)	F (Gm.)	C (Gm.)	Na (mg.)	Cholesterol (mg.)	Cal.
(1) Defined fat, low cholesterol, low sodium (1.25 cal./Gm.)							
Oil (corn oil, cottonseed oil, coconut oil)	22.0	—	22.0	—	—	—	198
Lesofac®	37.5	18.8	0.4	14.7	7.5	9.4	136
Dextrose	41.5	—	—	41.5	—	—	166
Water, to make	400.0						
		18.8	22.4	56.2	7.5	9.4	500
Distribution of calories		15%	40%	45%			
(2) Mixed animal fat, high cholesterol, low sodium (1.25 cal./Gm.)							
Frozen egg yolk	25.0	3.5	7.5	2.5	6.5	318.0	91
Butter (unsalted)	18.0	0.2	14.6	—	3.2	50.3	133
Lesofac®	30.0	15.0	0.3	11.7	5.8	7.5	110
Dextrose	41.5	—	—	41.5	—	—	166
Water, to make	400.0						
		18.7	22.4	55.7	15.5	375.8	500
Distribution of calories		15%	40%	45%			
(3) Evaporated milk formula with the same caloric distribution as human milk (1.50 cal./Gm.)							
Corn oil (Mazola)	12.5	—	12.5	—	—	—	116
Evaporated milk (Borden)	175.0	12.0	14.0	17.5	175	47.6	243
Dextrose	34.5	—	—	34.5	—	—	141
Water, to make	333.3						
		12.0	26.5	52.0	175	47.6	500
Distribution of calories		10%	48%	42%			

for homogeneity of fat content by countercurrent distribution—a labor that was economical in relation to the study because it defined the dietary fat for many days of intake.

Evaporated milk is a convenient source of protein, but it introduces a poorly-defined mixture of proteins, fats, minerals, and vitamins. Lesofac® meets the needs of studies requiring

could not be ground and dispersed into a stable emulsion.

Dextrose has been used because it is less sweet than sucrose. Lactose caused gas and loose stools, and after a week had crystallized out of stored formulas. Starch produced an indigestible glue-like pudding, even after partial hydrolysis by autoclaving.

Corn oil (Mazola*) proved to be a convenient source of fat. It is well defined in terms of fatty acid composition and is readily digested; although highly unsaturated it does not deteriorate rapidly at room temperature. Homogenates made with a refined fat are more stable than those that include milk or cream: corn oil formulas, for example, remained homogeneous after 12 weeks of storage at -15°C ., while fat globules separated from milk or cream formulas during a single week of cold storage. Butter, on the other hand, makes durable formulas. Apparently the natural emulsion of fat in milk is broken much more easily during cold storage than the artificial emulsions produced by a high pressure homogenizer; limitation of storage time of milk formulas must be reckoned against their economy and ease of preparation.

It is desirable to set the caloric value of formulas at a fairly high level, since reduction in the volume of liquid simplifies storage and consumption. Caloric concentrations in the range of 1.25 to 1.50 cal./Gm. proved satisfactory for oral use. More concentrated formulas are too rich to be palatable but are suitable for tube feeding: a mixture of Lesofac®, corn oil, and dextrose, similar to No. 1 in Table I but containing relatively less protein and water (2.0 cal./Gm., P 10%, F 40%, C 50%), flowed by gravity through a polyethylene tube 30 inches long and 2.1 mm. outer diameter (size 8 French) at a rate of 5 ml./min. This formula was administered by tube to one undernourished patient with cirrhosis who was unable to take adequate food by mouth. She received 57 cal./Kg., given in six equal doses each day, without gastrointestinal distress.

Mineral intake presented no problem with milk formulas, except for the need of an iron supplement when the experiment lasted a

month or more. Sodium was restricted in certain studies by substitution of Lesofac® for milk, but otherwise the mineral contents of the two formulas were similar. A capsule of mixed vitamins* given as a daily supplement brought the intake of known essentials above minimum requirements.

Bland formulas have proved to be more acceptable than flavored. Our initial use of coffee or chocolate syrup has been discontinued. Chromic oxide has been suspended in some formulas as an inert marker (1 mg. per ml. formula); it remained well mixed after freezing and thawing. Methyl cellulose (4 mg. per ml. formula) was added in some cases to provide residue.

PREPARATION

A Waring blender suffices for the preparation of formula for one or two patients, but, if studies are to be carried out on a larger scale, it is more efficient to homogenize formulas in larger lots and to store the bottled formulas in the frozen state. Moreover, formulas made with a high-pressure homogenizer are much less viscous than those made with a Waring blender; the viscosity of oral formulas is of relatively little importance, but is critical if the formula is to be fed by tube. At the present time we prepare formulas in 40-Kg. batches; two people can process at least 6 batches in one day—enough to feed about fifteen patients for a week. The cost of these operations (materials and salaries of personnel) is less than one-tenth of that required to run a conventional metabolic kitchen.

Equipment (total cost about \$1000): (1) a Toledo scale of 45-Kg. capacity with double-beam counterbalance, Model 2081; (2) two aluminum tanks of 10-gallon capacity with outflow spigot, one in which to premix the ingredients on the scale and the other to receive the emulsion from the homogenizer; (3)

* Mazola (Corn Products Refining Co.), manufacturer's analysis as follows: Glycerides 98.1%, non-saponifiable matter 1.9%, free fatty acids 0.03%, phospholipids—trace; iodine number 125; component fatty acids—linoleic 56.2%, oleic 30.1%, palmitic 9.9%, stearic 2.9%, hexadecenoic 0.5%, myristic 0.2%, above C_{18} 0.2%; component glycerides: mono-oleo-dilinolein 49.2%, mono-saturated-dilinolein 34.2%.

* Unicap (Upjohn), manufacturer's analysis as follows: vitamin A—5000 U.S.P. units, vitamin D—500 U.S.P. units, ascorbic acid—37.5 mg., thiamine hydrochloride—2.5 mg., riboflavin—2.5 mg., pyridoxine hydrochloride—0.5 mg., calcium pantothenate—5.0 mg., nicotinamide—20 mg., folic acid—0.25 mg., vitamin B₁₂—1 μg .

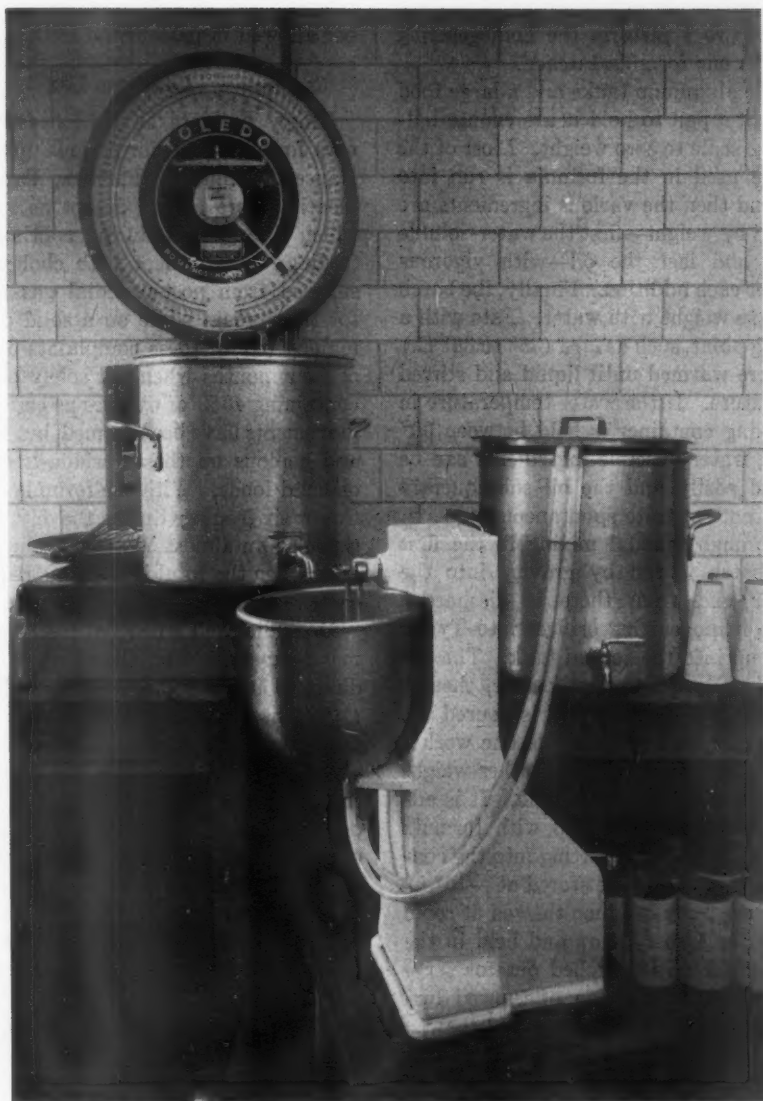


Fig. 1. Equipment used for homogenization of formula in 40-Kg. batches. Ingredients are added by weight to container on scale and premixed with food whipper. Mixture flows into homogenizer bowl, and homogenate is forced through tubing into container on right. Cartons are filled and stored in deep freeze until thawed for use.

a Logeman homogenizer, Model A40, with special outflow nozzles, Model 40; (4) paraffin-coated conical containers, pint or quart sizes (Sealright Kones), with flat, heavy paper disc stopper. Figure 1 pictures the homogenizing equipment in our formula kitchen.

One of the aluminum tanks and a large food whipper with a pan to hold it are counterbalanced on the scale to zero weight. Most of the water to be used in the formula is run into the tank, and then the various ingredients are measured in by weight—first the water-soluble ingredients and last the oil—with vigorous stirring after each addition. Finally, the batch is made up to weight with water. Fats with a high melting point, such as lard (35° to 38° C.) or butter, are warmed until liquid and stirred into the mixture. If the water temperature in the pre-mixing container is held between 30° and 37° C., water-miscible ingredients can be incorporated easily and the oil subsequently added does not separate spontaneously.

After thorough manual mixing in the first tank, the batch is run by gravity into the homogenizer and from there is discharged through the homogenizing orifices into Tygon tubing and up into the second tank. The entire batch is allowed to accumulate, then is stirred to assure uniformity and is poured out into paraffined containers. While one worker fills and caps the containers, the other weighs out a new batch into the first tank. It is advantageous to stamp each cap with formula number and date before inserting into the containers. The containers are stored at -15° C. until required. They are then thawed at room temperature for 4 to 6 hours and held in the ward refrigerator until weighed out for serving that day. The emulsion of thawed formulas is broken on refreezing; unused thawed containers are discarded at the end of each day.

Bacteriological studies of each batch have been made. Loopfuls of undiluted formula taken immediately after preparation and samples of the basic ingredients were streaked on blood agar and eosin-methylene blue pour plates. In all cases the processed formulas showed an increased growth of air-borne organisms as compared to the ingredients, but

in no instance have any pathogens been recovered. Storage at -15° C. and subsequent thawing had no significant effect on the colony counts, which always were far below the number allowed in pasteurized milk.

CLINICAL USE

Thirty patients have been fed completely on a formula basis for periods up to 16 weeks. Nausea, vomiting, diarrhea, flatulence, and bloating were absent except as rare episodes which disappeared during continued formula feeding. One patient with cholelithiasis had suffered from post-prandial gas and fullness for three years while on a solid diet, and remained free of these complaints over a period of four months when fed solely on a formula containing 40% of calories as corn oil. Bowel movements have been formed, but less frequent and copious on these residue-free diets than on solid foods. With the formula divided into five or six feedings during the day, the patients reported an almost constant feeling of satiety, even when the total intake was reduced to 600 calories per day.

Dogs did well when fed solely on formulas in an experiment on the effect of dietary sodium. The low sodium formula (No. 1, Table I) was used as a simple means of limiting intake, the same formula with added sodium chloride (2.1 Gm./L.) being used as a control. Twelve dogs took the feedings well for periods of 2 to 10 weeks, held steady weights or gained, had no diarrhea, and seemed in good general health.

Since it is possible by this technique to eliminate daily variation of the diet, fluctuations of body weight from day to day are minimized. As examples, the daily weight records of four hospitalized patients can be cited in terms of means and standard deviations: 47.9 ± 0.15 Kg. (30 days), 44.9 ± 0.20 Kg. (23 days), 58.1 ± 0.20 Kg. (42 days), and 64.0 ± 0.10 Kg. (24 days). We have not been able to achieve this degree of stability with conventional diets, even when these were served from a metabolic kitchen.

Great demands are put upon the staff of a metabolic kitchen, as well as upon the patient, in any experiment needing exact and simul-

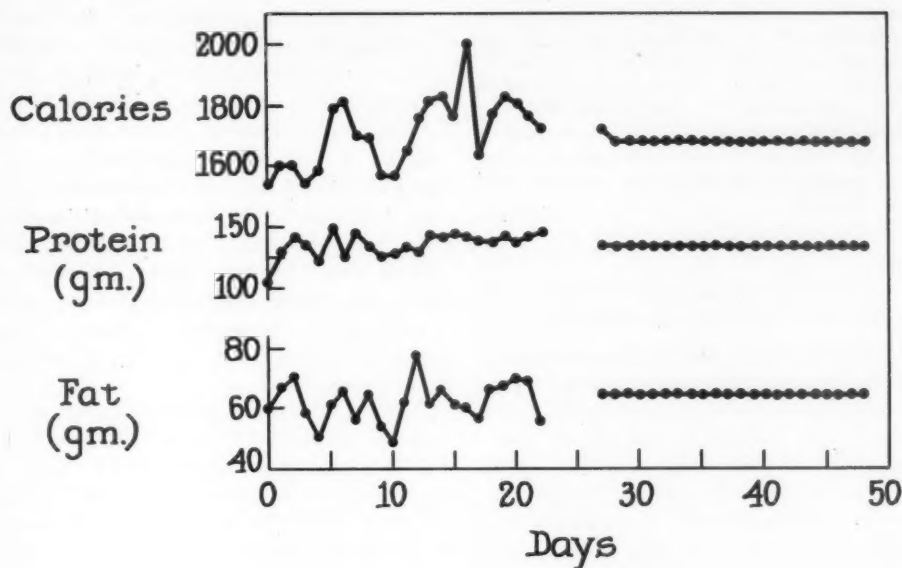


Fig. 2. Dietary intake of a patient fed mixed natural foods (day 0 to day 22) contrasted to liquid formula (day 27 to day 48).

taneous control of several different dietary variables: calories, fat, carbohydrate, protein, minerals, vitamins, and possibly other factors. Figure 2 contrasts the variations encountered in one experiment which started with the feeding of mixed natural foods and ended with the use of formulas.

The digestibility and high caloric value of liquid formulas suggest that they might be useful in the treatment of malnourished patients. To date, however, our main experience has been limited to the feeding of patients who were either normal or overnourished.

SUMMARY

Oral formulas as a sole source of nutriment proved to be valuable in a variety of metabolic studies. Patients had no difficulty in taking liquid feedings for periods up to 16 weeks. Dogs, in one experiment lasting 10 weeks, maintained weight or gained. As compared to mixed natural foods, formulas have the advantages of constant and defined composition, economy, and ease of preparation. A few basic formulas can meet the needs of various

metabolic studies. The three most useful in our experience are described.

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RESUMEN

El uso de fórmulas líquidas administradas por vía oral en los estudios metabólicos

Las fórmulas orales como fuente alimenticia única han demostrado su valor en una varie-

dad de estudios metabólicos. Los pacientes aceptaron sin dificultad alguna la alimentación líquida durante períodos de hasta 16 semanas. Perros, en un experimento continuado por un período de 10 semanas, mantuvieron o aumentaron su peso. En comparación con los alimentos mixtos naturales, las fórmulas ofrecen las ventajas de su composición constante y definida, economía, y facilidad de preparación. Unas pocas fórmulas básicas pueden satisfacer los requerimientos de diversos estudios metabólicos. Se describen las tres fórmulas que han sido las más útiles en la experiencia de los autores.

The Food Consumption of Juvenile Diabetics

Evaluation of Diets Used at Home and at Summer Camp

By HARRY G. JACOBI, M.D.*

With the technical assistance of MILDRED KAUFMAN, M.S.,† AND TAMI OGATA, A.B., M.S.†

IN A PREVIOUS report on nutritional studies of diabetic children attending summer camp¹ we mentioned the observation that the actual food consumption at home by many of these children was not always that which was represented by the figures furnished to us on the camper's application for admission to camp. The desire for more accurate information regarding this prompted us to undertake a careful analysis and calculation of the food consumption at home.

To carry out such studies it was of course necessary to interview each child and attempt to make the necessary calculations from the information thus furnished. This, we felt, would be the best way of learning just what the caloric intake actually was and how it compared with the diet prescription ordered by the referring physician. Information was also obtained regarding the insulin dosage and the level of diabetic control that was maintained while on these home diets as judged by the degree and persistence of glycosuria.

We were also interested in the problem involving those of our children who had not received at any time any definite instructions regarding their food intake; and, finally, we were particularly anxious to obtain information regarding that group of children who were on the so-called "free diet" regime.

Before considering these data, however, certain qualifying statements must be made. First, we were able to carry out this investigative work only with the older children (10-17 yrs.). Many of the younger group had to be excluded because it was difficult to confirm their reliability. Furthermore, it must be realized that there are differences inherent in the various methods of caloric calculation used, which may lead to variations of as much as 20 to 30 per cent in the total figures. Therefore, it is clear that the calculations of the home consumption diets are in reality only approximations.

These particular studies were possible in a total of 120 cases (62 girls and 58 boys) out of the entire group of 155 attending camp during the summer of 1951. The remainder of the group were excluded from the survey because their data were not considered to be sufficiently reliable to warrant inclusion.

OBSERVATIONS

Table I shows the relation between the prescribed and actual (as calculated) home diet of the 58 boys and 62 girls of our series. It can be seen that only about one-fifth of the boys and one-third of the girls followed their prescribed diet. A significant number apparently consumed a diet about one and one-half times the caloric intake prescribed by their physician. A high percentage (29.3 per cent of the boys and 33 per cent of the girls) followed no dietary restriction and are here classified as on a "free diet."

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TABLE I
Analysis of Calculated Home Diet Consumption
Carried Out on 58 Boys and 62 Girls of Our Series

Type of diet	Boys		Girls	
	No.	%	No.	%
As prescribed	11	19	22	35
Less than prescribed diet	0	—	2	3
1½ times prescribed diet	22	38	14	23
2 times prescribed diet	7	12	1	1.5
2½ times prescribed diet	1	1.7	2	3
3 times prescribed diet	0	—	1	1.5
Free diet	17	29.3	20	33

It was of particular interest to analyze the food intake of children on a so-called "normal," "free," or "unrestricted" diet. The results of this survey in the 37 children on a free diet are presented in Table II. Of the total,

TABLE II
Analysis of Cases on "Free" or "Uncontrolled" Diets

	Caloric calculation of actual food intake							
	Normal intake		1½ times normal		2 times normal		2½ times normal	
	No.	%	No.	%	No.	%	No.	%
Boys	8	47	3	17	4	24	2	12
58 total								
17 "free"								
Girls	12	60	5	25	3	15	—	—
62 total								
20 "free"								
Total on "free" diet:	20	54	8	22	7	19	2	5
37								

about half (54 per cent) were found to have been taking the correct amount of food warranted by their particular age, weight, and physical activity. About one out of every four of these ingested two or more times the caloric intake indicated on clinical grounds. The distribution was somewhat different between boys and girls, in that, on the whole, the girls were less likely to eat amounts in excess of their actual requirements. (In all cases the normal values used in the calculations are those given for ideal body weight and are based on figures suggested by the Food and Nutrition Board of the Nutritional Research Council.)

It is significant that there were 35 boys and 15 girls who claimed to have taken more than 3000 calories while at home, whereas at camp, where they were presumably more active, not

a single child was fed more than 2900 calories.

Of the 33 boys in this "over 3000 caloric group," 13 showed a gain, 14 lost, and six showed no change in weight. All of the 14 who lost weight were definitely overweight at the time of admission to camp.

Similarly, of the 15 girls in this group, three gained, ten lost, and two had no change in weight at the end of their camp stay. Practically all the girls in this category had been definitely overweight when they arrived at the camp.

INSULIN DOSAGE

In most instances, the insulin dosage at the start of the camp period was reduced from that of the home dosage. As can be seen from representative data (Table III) on the 12-

year-old group, in some cases the final insulin schedule was even lower, while in others higher, than the dosage at the beginning of the camping period. In very few cases in the entire group did we have to increase the insulin dose above the amount which had been prescribed for home administration.

The reason for the generally lower insulin dosage at camp is probably the very poor control of the diabetes in a number of these children before coming to camp, a finding which we feel is valid although we cannot quantitate the degree of control. Since, in many instances, the children were eating a lower carbohydrate diet in camp, they could be better controlled on smaller amounts of insulin aided by increased physical activity.

TABLE III
Data on a Representative Group (12-Year-Old Children)

Case no.	Duration of diabetes, yrs.	Diet										Insulin dosage*									
		Home prescribed					Estimated actual consumption					Camp									
		C			P		F		Cal.			Beginning			Ending		Beginning		Ending		
		C	P	F	Cal.	C	P	F	Cal.	C	P	F	Cal.	C	P	F	Cal.	Home	*	Beginning	Ending
MALES																					
35	9	190	80	80	1800	289	136	164	3176	200	100	100	2100	300	120	110	2670	N. 60		N. 40	N. 52
36	5	200	150	90	2210	258	126	147	2859	300	120	100	2100	325	120	100	2100	N. 30		N. 22	N. 30
37	4	200	150	90	2210	474	174	252	4860	325	120	120	2860	325	120	120	2860	N. 30		R. 18,	P. 10, M.
38	3	200	90	80	1880	219	121	150	2710	200	100	100	2100	200	100	100	2100	R. 25,	M.	N. 48	N. 50
39	6				"Free,"	169	95	104	1962	300	120	110	2670	250	110	110	2400	N. 40		N. 28	N. 40
40	11	140	90	90	1730	225	123	181	3021	200	100	100	2100	200	100	100	2100	R. 18,	M.	R. 18,	P. 12, M.
41	1/2	350	100	130	2970	365	140	181	3649	325	120	120	2860	325	120	120	2860	R. 24,	M.	R. 11,	P. 11, M.
FEMALES																					
108	9/4	150	100	80	1720	211	100	100	2144	160	95	90	1800	160	95	90	1800	P. 32		P. 22	P. 16
109	2				"Normal,"	291	97	100	2452	250	110	110	2400	250	110	110	2400	N. 25		N. 18	P. 34
110	1 1/2	250	95	68	1992	302	110	118	2710	200	100	100	2100	200	100	100	2100	R. 26		R. 18	P. 8, M.
111	1	180	90	100	1980	250	102	115	2443	200	100	100	2100	200	100	100	2100	R. 24,	M.	R. 18,	P. 8, M.
112	8				"Free,"	345	128	128	3044	250	110	110	2400	250	110	110	2400	R. 24,	P. 12, M.	R. 22,	P. 12, M.
113	3				"Regular,"	336	120	136	3048	200	100	100	2100	200	100	100	2100	R. 25,	M.	R. 40,	P. 45, M.
114	3	200	90	70	1790	244	104	125	2517	200	100	100	2100	200	100	100	2100	N. 42		N. 30	N. 56

* P = PZI; N = NPH; R = Regular; M = Mixture.

DISCUSSION

There were several significant facts which were learned as a result of our analysis of the comparison of the prescribed home diets with the calculated actual daily home food consumption and the final camp diets. Examination of our data reveals that most of the home diet prescriptions actually did not deviate very much from the final camp diet. However, the calculated average daily home food consumption showed an entirely different picture, as shown in the analysis contained in Table III. It was found that most of the children were consuming carbohydrate intakes much in excess of their diet prescriptions. They were eating not only extra bread, fruit, and milk, but also some of the more concentrated carbohydrates such as ice cream, sweetened desserts, cakes, cookies, and candies. This was a more common practice among the 14- to 17-year age groups than among the younger age groups. Data from the remaining groups for which records are available show that there was much less deviation in the carbohydrate intakes than among the older group. Furthermore, many of the home diet prescriptions were actually found to be insufficient in total calories, and so some of the children appear to have compensated for this deficit by intakes in excess of their diet prescriptions.

We found that most of the children (and evidently this was also true of their parents) had not received adequate diet instructions either from their physicians or from dietitians in the various hospitals or clinics. They had little knowledge of the relative carbohydrate values of food and other exchange values. Several of the girls, for example, honestly felt that they were sticking quite closely to a prescribed diet, but actually, according to our estimations, were off as much as 1000 to 3000 calories a day.

In trying to obtain home diet histories from these diabetic children, it was expected that since they were on restricted diets, food would have great significance for them. They would be expected to be more or less conscious of what they did eat each day, and when they were breaking their diets. It was found that,

in general, children on restricted diets were conscious of the food they ate and followed a rather consistent pattern in their meals. However, these children often ate concentrated sweets as extras without realizing that by so doing they were completely overcoming the efforts to control their caloric intake. The impression gained, however, was that though some of these children were not following their prescribed diets, they were consistently eating the same kind of diet every day. They were being controlled on this diet which, in reality, was higher than their physicians realized.

We had no difficulty whatsoever in bringing the children of this group in line so that they were receiving the diets indicated for their age, weight, and height standards. They appeared to be just as well pleased with this routine as with their "free diet" and we did not hear of any difficulty arising because of the change.

As a result of this analysis we now have some idea of the proportion of juvenile diabetics coming from the New York area that are being treated on "free diets," and also what such "free diets" have actually turned out to be when subjected to careful study and evaluation. Results of studies similar to those presented above may be different for other parts of the country, and we feel that an analysis should be undertaken in different areas for a comparative study.

SUMMARY

An analysis and estimation of diets consumed at home prior to coming to a summer camp for diabetic children was attempted on 62 girls and 58 boys out of a total camp population of 81 girls and 74 boys.

Most of the children were found to be consuming carbohydrate (and calories) greatly in excess of their diet prescriptions. In many instances, however, the prescribed home diets were considered to be actually insufficient in total calories to meet the energy needs of active and rapidly growing children. Most of the children and their parents had not received adequate diet instructions from either their physicians or from dietitians in hospitals and clinics. They had little knowledge of

the relative carbohydrate values of foods or of exchange values.

An analysis is presented of all children who were on "free diets" prior to coming to camp, to study the actual deviation of these from the so-called average food requirements as established by accepted standards. About half of a group of 37 children on a "free diet" consumed a diet considered "normal" and adequate for their needs. The others ingested increasing amounts of food in excess.

Data are presented showing the prescribed home diet, the actual home diet, as obtained by questioning, the final camp diets, and the corresponding insulin dosages in a representative group of campers.

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RESUMEN

El consumo alimenticio de diabéticos jóvenes. Apreciación de las dietas empleadas en casa y en un campo de verano

Un análisis de las dietas consumidas en casa antes de llegar a un campo de verano para niños diabéticos fué intentado en 62 muchachas y 58 muchachos de un total de 81 muchachas y 74 muchachos asistiendo al campo.

Se descubrió que la mayor parte de los niños consumían cantidades de hidratos de carbono (y calorías) muy en exceso de las indicadas en sus recetas dietéticas. En muchos casos, sin embargo, las dietas caseras impuestas fueron juzgadas como realmente insuficientes en calorías totales para cumplir las necesidades energéticas de niños activos en el período de rápido crecimiento. En la mayoría de los casos, ni los niños ni sus padres habían recibido instrucciones dietéticas adecuadas, sea de sus médicos sea de los servicios dietéticos de los hospitales y clínicas.

Se presenta un análisis de todos los niños consumiendo dietas "libres" antes de llegar al campo, con objeto de estudiar la verdadera desviación de dichas dietas de los llamados requerimientos alimenticios medianos establecidos según los *standards* aceptados. Alrededor de la mitad de un grupo de 37 niños siguiendo una dieta "libre" consumía una dieta considerada como "normal" y adecuada a sus

necesidades. Los demás ingerían cantidades cada vez mayores de alimentos en exceso.

Se presentan datos sobre la dieta casera impuesta por el médico, la dieta casera efectivamente consumida (datos obtenidos por interrogación), las dietas últimamente establecidas en el campo, y las dosis correspondientes de insulina en un grupo representativo de niños.

Editorial

Should Vitamin-Mineral Products Be Standardized?

The Food and Nutrition Board of the National Research Council has been requested by the Food and Drug Administration to provide answers to certain questions in regard to the use of vitamin-mineral products, including the desirability of establishing standards for such products. The National Research Council (Food and Nutrition Board) has been reported to have accepted this commission and the Executive Committee of the Board is reported to have a draft of reply under consideration. Since the questions raised indicate that the Food and Drug Administration is dissatisfied with the present labeling situation and desires a better system of control, and since the answers to these questions could very well drastically affect the availability and utilization of vitamin-mineral products, we are taking this editorial space to bring these questions to your attention, along with our answers.

Question: Are there conditions which make it necessary or desirable to supplement the diet with certain combinations of vitamins?

Answer: Yes.

Question: If the answer to this question is yes, what are these conditions and what vitamins are needed for these purposes?

Answer: The conditions which make vitamin supplementation necessary include: Poor dietary habits, unavailability of certain foods, diminished intake of certain foods for any reason, interference with intestinal absorption or the destruction of vitamins in the intestinal tract, increased metabolic requirements, impairment in utilization or storage, and increased loss or excretion of

nutrients from the body. The vitamins and minerals needed for the management of these conditions will vary from condition to condition and with various diets.

Question: To meet such needs, what quantities of vitamins should be supplied in a daily supplement?

Answer: The amounts needed as a daily supplement vary widely. In general, supplemental vitamin requirements can be met within a range of one-quarter to three times the Recommended Dietary Allowances.

Question: Should the quantity of each vitamin be related to the quantity of that vitamin necessary to meet normal requirements?

Answer: In general, vitamin and/or mineral mixtures designed to supplement inadequate diets should bear some relation to the daily requirements. However, the quantity of any particular vitamin or mineral in vitamin-mineral preparations should also bear some relation to the probable adequacy or inadequacy of that vitamin or mineral in the diet of the individuals for whom the product is intended. Also, since supplemental vitamin preparations are often intended for the use of individuals with greater than normal requirements, provision must be made for products containing greater amounts of certain vitamins than the Recommended Dietary Allowances. In other instances it may be desirable to omit certain vitamins from multiple vitamin preparations, i.e., individuals with leukemia may require vitamin supplements from which folic acid has been omitted.

Question: Will the establishment of standards help in preventing the consumer from being

misled by representations made for products of the type now on the market?

Answer: Pharmaceutical vitamin preparations are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and are properly classified as drugs. As such, the Food and Drug Administration has no authority to establish standards of identity. In order to do so, the Food and Drug Administration would have to classify pharmaceutical vitamin preparations as foods, and there is some doubt that the Food and Drug Administration has authority to do this under the present Food, Drug, and Cosmetic Act. There is no reason to believe that establishing standards would help in preventing the consumer from being misled. The present labeling requirements are for practical purposes adequate to protect the consumer. The nefarious practices which appear to concern the Food and Drug Administration involve a very small minority of the industry, less than 5 per cent of the total pharmaceutical vitamin and mineral sales. The answer to this problem lies in strengthening the Federal Trade Commission and not in placing 95 per cent of the pharmaceutical industry in a regulatory straight-jacket that will still leave the offending minority just as free to make improper claims for their products. There is no problem of safety involved in the sale of supplemental vitamin and/or mineral products. The problem of adulteration is covered by the Federal Food, Drug, and Cosmetic Act. The problem of false or misleading claims is covered, in labeling, by

the Food, Drug, and Cosmetic Act; and, in advertising, by the Federal Trade Commission Act.

Question: Will the establishment of standards stand in the way of progress in proper use of vitamins?

Answer: If the Food and Drug Administration is allowed to decree specific formulae for vitamin preparations, both as to what may be contained therein and how much of each ingredient, it will tend to discourage the development and utilization of new vitamins and minerals and will result in the discontinuance of many useful combinations. It will deprive the physician of ready-made combinations and interfere with his professional prerogative to choose from a wide variety of medicines. The medical profession should strongly resist efforts to standardize the medication which they may prescribe. The standardization of vitamin formulae by the Food and Drug Administration would discourage research by the industry and would impede the progress of the science of nutrition.

At this time it is pertinent also to point out that there is absolutely no indication or justification for the Food and Drug Administration to make therapeutic vitamin preparations prescription items. Doing so would simply needlessly increase their cost and lessen their use.

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Some Thoughts Regarding Obesity

The clinician who concerns himself with nutritional and metabolic problems is confronted by many individuals whose presenting problem is that of excess weight. A fairly high percentage of such patients have convinced themselves, or have been convinced by others, that their obesity is "glandular," and that all the physician needs to do is to unravel their complex "glandular disorder," prescribe the necessary pill, and all will be well. The physician in turn is apt to be rather certain in his own mind that the patient has no endocrinopathy, and is obese for the good and sufficient reason that he or she consumes an excessive amount of food. In terms of fundamentals, there is no question that the latter analysis is correct.

The tendency on the part of most capable physicians is to approach an obese patient about as follows:

1. Patient, Mary Smith, is obese.
2. Therefore, patient Mary Smith eats excessively.
3. Patient Mary Smith, on the basis of her height and average daily activity, has a total daily caloric requirement of 1800 calories.
4. Therefore, patient Mary Smith if placed on a diet containing 1000 calories will lose at a predictable rate.
5. If patient Mary Smith fails to lose at the aforesaid predictable rate, she is "cheating."

The foregoing logic on the surface appears to be irrefutable. Unfortunately (in a clinical sense), there appear to be certain flaws. The majority of Mary Smiths who fit into a category similar to the above *will* lose weight at a predictable rate when placed on a diet, the caloric content of which is significantly below that of their estimated daily requirements. In a certain number, however, the dietary calories must be not only below the theoretical requirement, but rather startlingly below such a figure.

Illustrative of this is a study carried out under quantitatively controlled conditions on the metabolic ward in this Institute more than two years ago.¹ A young obese girl was

admitted to the metabolic ward for evaluation, with a story of obesity unresponsive to the usual dietary measures. Her dietary history indicated a more than average enjoyment of food, and a relatively high caloric intake in childhood. It was our feeling, therefore, that her alleged unresponsiveness to specific diets was actually a matter of never having adhered to a prescribed diet. She was placed on a quantitatively constant formula diet, administered hourly throughout the 24 hours via nasogastric tube. On an 800 calorie diet, after some initial weight loss, she progressively approached weight equilibrium. After a period of additions of increments of fat (to determine the antiketotic properties of protein), the diet was reduced to 600 and finally to 400 calories.

At the 400 calorie level, if all the diet was derived from protein, minimal weight loss occurred. If all the 400 calories were derived from carbohydrate or carbohydrate plus fat, rapid weight loss occurred. During the intake of 400 protein calories, the patient was in positive nitrogen balance in an amount averaging more than one gram daily. With the 400 calorie carbohydrate, or carbohydrate-fat intake, she was in negative nitrogen balance in an amount averaging about four grams per day. These findings are shown in Figure 1. Three other similar patients have been studied under semi-quantitatively controlled conditions since that time, and have appeared to follow much the same pattern.

One is able to explain the above observations on the basis of one or both of two assumptions:

1. The first assumption is that some individuals have an unusual ability to conserve protein; i.e., the average individual receiving only 400 calories daily, even though all of it be in the form of protein, will not be in nitrogen equilibrium. Since this patient was receiving no carbohydrate, and after the first few days had exhausted all of her endogenous carbohydrate stores, one must conclude that she had the ability to catabolize fat with a

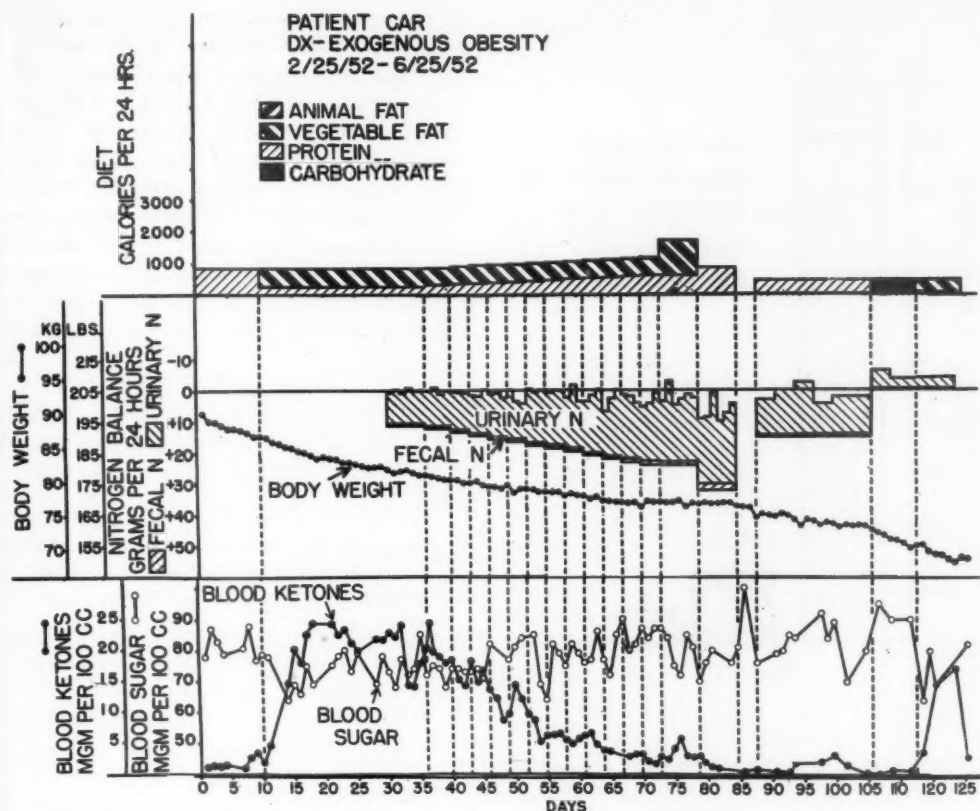


Fig. 1. Long-term balance in an obese individual. The weight and nitrogen balance changes during days 87-124 are of particular interest from the standpoint of this discussion.

high degree of efficiency, with consequent protein conservation. Since protein tissue is 80 per cent hydrated, and, therefore, has a caloric equivalence of approximately one calorie per gram, and fat tissue is 10 per cent hydrated and has a caloric equivalence of about eight calories per gram (Figure 2), this patient (whose calculated daily caloric requirement was 1700 calories) should have lost approximately 130 grams per day while receiving 400 protein calories. She actually lost 150 grams per day, the difference, presumably, being attributable to salt and water loss. Such a patient, if she conserved protein with equal efficiency on a pure protein diet having an 800 caloric equivalence, could actually gain weight until her own fat stores were exhausted.

2. The second assumption is that the net

mechanical efficiency of the body may vary appreciably between individuals. In this connection, one might point out the very obvious difference in heat loss during physical exertion in the trained athlete as compared to the average office worker. Benedict and Cathcart,² reviewing the subject of mechanical efficiency of the animal body, noted that in their subjects, average net efficiency might vary from 20.4 to 25.2 per cent. One does not need to invoke such an assumption in the patient noted above.

The above comments are not intended to suggest for a moment that the mainstay of the clinical approach to weight reduction is not the use of a simple, relatively high protein, low caloric diet. They are rather to point out that there are endogenous factors, as yet by

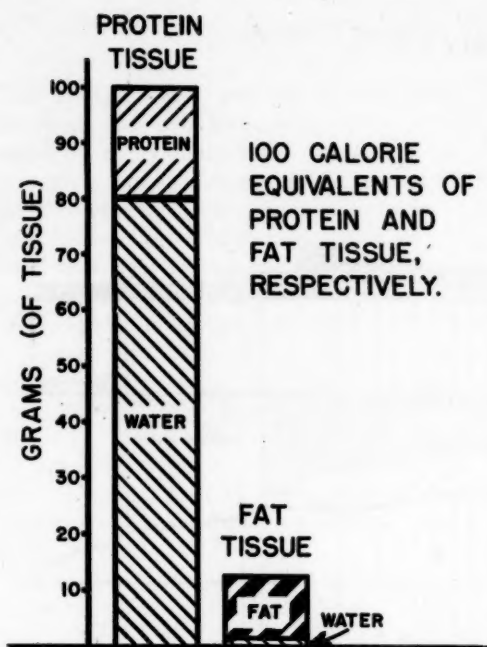


Figure 2

no means well understood, which on occasion will enable two individuals of approximately the same size and age, having "normal metabolic rates," and indulging in about the same amount of daily activity, to move in different directions in regard to weight, even though their food consumptions be identical; and further to point out that "a calorie is not necessarily a calorie" insofar as weight reduction is concerned; i.e., the qualitative make-up of a diet, as well as its caloric equivalence, may influence in a major way the pattern of weight change.

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Dietotherapy

THE LOW CHOLESTEROL, LOW FAT DIET

By CORINNE H. ROBINSON*

PERHAPS no diet is receiving more careful scrutiny by the medical profession than the low cholesterol, low fat diet. There is by no means agreement as to the value of the diet or its quantitative definition. Even if this type of diet is assumed to be effective, knowledge is lacking about all the modifying conditions which might increase or nullify its efficacy. Nevertheless, increasing numbers of physicians are prescribing the diet, the essential features of which are reviewed here. The intelligent use of the diet demands that its characteristics be understood, and that each patient's response to the diet be evaluated frequently.

TERMINOLOGY

A low cholesterol diet is not synonymous with a low fat diet. Vegetable fats, for example, do not contain cholesterol, although they may serve as precursors for the synthesis of cholesterol in the body. On the other hand, organ meats are significant sources of exogenous cholesterol, but, since they are low in fat, they would be permissible in a low fat diet. The diet discussed here is low in both cholesterol and fat. It will be noted in the list of foods to avoid that separate categories have been set up for foods high in cholesterol and high in fat. Some foods obviously fall into both groupings. It is thus possible so to modify the diet described here that it is low in exogenous cholesterol but contains more liberal allowances of fat.

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CHARACTERISTICS OF THE DIET

Cholesterol Content

The cholesterol values reported for foods by Okey¹ have been used widely. A recent compilation of values has also been made by Lange.² Cholesterol is present to some extent in all animal tissues but occurs in greater concentrations in active tissues and in body fats. Thus, liver, brains, heart, kidney, and sweetbreads contain especially large amounts of cholesterol. Likewise, egg yolk, fish roe, and caviar are abundant sources. Whole milk, butter, cream, cheese, and ice cream contain appreciable amounts, as do all meats, the concentration in fatty meats being somewhat higher than in lean.

The sterols in plant foods are not absorbed from the gastrointestinal tract, and therefore it is possible to use most plant foods without restriction.

The normal diet varies in its cholesterol content, depending upon the choice of foods. It may contain as little as 200 mg. daily for the person who does not eat eggs, organ meats, and excessive amounts of butter; or it may be as high as 1600-1800 mg. if one eats several eggs, liver, fatty meats, and butter. If one assumes the use of the basic diet described in an earlier paper of this series,³ the cholesterol content would be approximately as follows:

	Amount	Cholesterol
		mg.
Whole milk	3 cups	100
Egg	1 whole	300
Meat (excluding organ meats), lean	3 ounces	50
Cheese, whole-milk	1 ounce	50
Butter	2 tablespoons	85
	TOTAL	585

Fat

It has been estimated that the endogenous production of cholesterol is ten to twenty times as great as the dietary cholesterol. Since cholesterol can be easily synthesized from fat, it is usually considered advisable to restrict both animal and vegetable fats. Fat levels as low as 15 to 25 Gm. daily have been employed by some.

Dietary Adequacy

Normal levels of protein are permitted, that is, 1 Gm. per Kg. of body weight. Since the fat is greatly reduced, it becomes necessary to increase sharply the carbohydrate intake to maintain caloric balance unless, as often happens, weight reduction is also indicated. A satisfactory intake of essential minerals and vitamins can be achieved with proper planning. It should be recognized that, with the omission of all animal fats and all organ meats, the vitamin A is derived from carotene. Whenever inability to convert carotene to vitamin A is suspected, a supplement of vitamin A should be prescribed.

Acceptability

One of the chief obstacles to the use of the diet is its reduced palatability. The patient is not only denied the delicate flavors added with butter or margarine as a spread for bread or a seasoning for vegetables, but is considerably limited in his choice of foods. For example, the omission of egg yolk, whole milk, and butter or other fats means that a goodly number of prepared foods are also contraindicated—many puddings, ice cream, pastries, cakes, cookies, and quick breads, to mention but a few.

Skim milk is not liked by many, but usually the individual becomes accustomed to it and in time may even prefer it to whole milk. Such a simple expedient as serving the milk ice cold deserves emphasis because so often this precaution is not taken. Skim milk may be used successfully in the preparation of cornstarch puddings (without egg), in cream soups thickened with a little flour-water paste (no

fat), in cocoa-flavored beverages, and in the preparation of fruit ices.

Cooked vegetables may be seasoned with salt, pepper, or a variety of herbs and spices. A dash of nutmeg on green beans, peas cooked with mint, corn with tomatoes, just a speck of mace with potatoes mashed with double-strength skim milk (made from nonfat milk solids) suggest a few possibilities for adding flavor appeal when fats are missing. Occasionally, vegetables may be cooked in a small amount of fat-free broth for taste variety.

LOW CHOLESTEROL, LOW FAT DIET

Include these foods each day:

- 3 cups skim milk
- 5 ounces lean beef, veal, or lamb; poultry; or fish
- 1 serving whole-grain or enriched cereal
- 6 slices whole-grain or enriched bread
- 1 medium potato
- 1-2 servings leafy green or yellow vegetable
- 1 serving other vegetable
- 1 serving citrus fruit or other source of ascorbic acid
- 2 other fruits

For additional calories use: sugar, jelly, jam, or greater amounts of vegetables, fruits, cereals, or breads.

Nutritive value of listed foods: Cholesterol, 75 mg.; protein, 75 Gm.; fat, 25 Gm.; carbohydrate, 220 Gm.; calories, 1400; calcium, 1150 mg.; iron, 12 mg.; vitamin A, 6200 I.U.; thiamine, 1.5 mg.; riboflavin, 2.3 mg.; niacin, 16 mg.; ascorbic acid, 145 mg.

AVOID THESE FOODS:

High in Cholesterol

Brains	puddings, custard, egg
Butter	noodles, griddle cakes,
Caviar	waffles, etc.
Cheese—all except skim-	Heart
milk cottage	Kidney
Cream	Liver
Egg yolk	Mayonnaise
Fish roe	Milk, whole
Foods containing egg	Shellfish: oysters, clams,
yolk, butter, whole	crabs, lobster, shrimp
milk, or cream: cake,	Sweetbreads
cookies, eggnog, pas-	Tripe
tries, pie, milk and egg	

High in Fat

Butter	Fats and oils, both ani-
Cheese, whole-milk	mal and vegetable:
Chocolate	lard, margarine, hydro-
Cream	genated fats, salad oils

Cream sauces
 Fatty meat: bacon, ham, pork, sausage, salt pork; mackerel, herring, fish canned in oil; duck, goose

Fried foods: doughnuts, fritters, griddle cakes, etc.
 Nuts; peanut butter
 Pastries, pies
 Salad dressings

The following menu pattern is one way in which the foods in the above list might be arranged:

PATTERN MENU	SAMPLE MENU
<i>Breakfast</i>	
Fruit, preferably citrus	Half grapefruit
Cereal	Oatmeal with sugar
Skim milk—1 cup	Skim milk
Bread—2 slices	Whole-wheat toast—2 slices
Jelly, jam, or marmalade	Orange marmalade
Hot beverage	Coffee, with sugar, if desired
<i>Luncheon or Supper</i>	
Clear soup, if desired	Consommé
Lean meat or cottage cheese	Sandwich:
Bread—2 slices	2 ounces lean roast beef
	2 slices rye bread
	Lettuce
	Prepared mustard
Green or yellow vegetable	Celery and carrot sticks
Skim milk	Skim milk—1 cup
Fruit	Fresh fruit cup

Dinner

Lean meat, poultry or fish
 Potato or substitute
 Green or yellow vegetable
 Bread—2 slices
 Jelly or jam
 Fruit or dessert
 Skim milk—1 cup

Baked flounder with Creole sauce
 Steamed rice
 Zucchini squash
 Bread—2 slices
 Grape jelly
 Angel cake with fresh strawberries
 Skim milk

SUMMARY

A low cholesterol, low fat diet which provides the recommended dietary allowances for the man or woman has been described. Since the value of this diet in vascular disease has not been established, and since it must be used indefinitely by those patients whom it may benefit, it is essential that the diet not be used indiscriminately. The patients for whom the diet is prescribed should be evaluated at frequent intervals to determine any possible benefits accruing from this regimen.

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2. LANGE, W.: Cholesterol, phytosterol, and tocopherol content of food products and animal tissues. *J. Am. Oil Chem. Soc.* 27: 414, 1950.
3. ROBINSON, C.: Food therapy begins with the normal diet. *J. CLIN. NUTRITION* 1: 150, 1953.

Nutrition News

* News of activities in the field of clinical nutrition should be submitted to the Editorial Office of the JOURNAL.

Nutrition-Blood Symposium

A symposium on the *Nutritional Aspects of Blood Formation*, sponsored by the National Vitamin Foundation, will be held at the University of Cincinnati on Friday, October 22, 1954.

The morning session will be under the chairmanship of Dr. Richard W. Vilter, Associate Professor of Medicine, College of Medicine, University of Cincinnati, and the afternoon session will be under the chairmanship of Dr. M. A. Blankenhorn, Professor of Medicine, University of Cincinnati, and Director of the Department of Internal Medicine, Cincinnati General Hospital.

The symposium is open to all interested physicians and scientists.

The following topics will be presented and discussed:

Iron Metabolism in Relation to Microcytic Hypochromic Anemia (Carl V. Moore, M.D.)

The Relationship of Copper, Cobalt and Trace Elements to Hematopoiesis (George E. Cartwright, M.D.)

Some Metabolic Interrelationships of Folic Acid, Vitamin B₁₂, and Ascorbic Acid (J. N. Williams, Ph.D.)

Interrelationship of Folic Acid, Vitamin B₁₂, and Ascorbic Acid in Patients with Megaloblastic Anemia (John F. Mueller)

The Absorption and Utilization of Vitamin B₁₂ (Robert F. Schilling, M.D.)

Relationships of Hormones to the Utilization of Essential Nutrients in Erythropoiesis (Roger C. Crafts, Ph.D.)

Antimetabolites and Antibiotics as Tools for Research on Blood Formation (Tom H. Jukes)

Stercobilin and Hematopoiesis (G. Watson James, III, M.D.)

Essential Nutrients in the Management of Hematopoietic Disorders of Human Beings—A Résumé (Richard W. Vilter)

Annual Arteriosclerosis Meeting

The American Society for the Study of Arteriosclerosis will hold its eighth annual meeting on October 31 and November 1, 1954, at the Sheraton Hotel, Chicago.

Among the papers which will be presented are:

An Evaluation of the Blood Lipids in Human Atherosclerosis: A Preliminary Report (Drs. Paterson, Cornish, and Armstrong)

Serum Lipids in Carefully Selected "Atherosclerotic" and "Normal" Males (Drs. Little, Shanoff, Van der Flier, and Rykert)

An Evaluation of the Effect of Choline and Inositol on the Clinical Course and Serum Lipids in Patients with Angina Pectoris (Drs. Jackson, Wilkinson, Meyers, Bruno, and Benjamin)

The Serum Cholesterol Level and Lipoprotein Pattern Following the Administration of Plant Sterols (Drs. Kuo and Joyner)

Effects of Prolonged Administration of Sitosol on Serum Lipids (Drs. Best, Duncan, Wathen, VanLoon, and Shipley)

Production of Hyperlipemia and Lipoid Infiltration of Intima and Media of Aorta by a High Fat, Cholesterol-free Diet (Drs. Steiner and Dayton)

The Effects of Certain Vegetable and Animal Fats on Plasma Lipids of Humans (Drs. Beveridge, Connell, Mayer, Firstbrook, and DeWolfe)

Further Experience with High Vegetable Fat Diet in Patients with Extensive Diabetic Vascular Disease (Drs. Kinsell, Cochrane, Smyrl, Fukayama, and Coelho)

A Preliminary Report on the Prevention of Necrotizing Arteritis in Dogs by B Complex Vitamins and a Possible Interpretation (Dr. Holman)

There will also be addresses by Dr. Carl J. Wiggers and Dr. Russell L. Holman.

Nutrition Briefs

CURRENT OBSERVATIONS OF CLINICAL INTEREST

URINARY nitrogen and sulfur were determined on samples from infants with acute nutritional disturbances. The amount of neutral sulfur, normally 5 to 11 per cent, reached a maximum of 65 per cent in the presence of acute nutritional disorders.

W. Friedel. *D. Ztschr. f. Verdauungs. u. Stoffwechselkrankheiten* 13: 17, 1953.

STUDY of the serum proteins before and after the administration of large doses of intravenous iron revealed no evidence of any disturbance of serum protein metabolism. It would seem that such "unphysiologic" amounts of iron have no untoward effect on the production of serum proteins and that a "blockade of the reticulo-endothelial system" need not be feared in the course of such therapy.

H. Overkamp. *Ärzt. Forsch.* 7: 478, 1953.

VITAMIN E is stated to have a favorable effect on carbohydrate metabolism in diabetes. The vitamin was administered orally (200 mg. daily for 10 days) to metabolically normal controls and to diabetics. The blood sugar response to glucose administration was studied before and after the treatment period. After vitamin E, the blood sugar curve showed lower peaks and shorter plateaus. Glycosuria was also favorably influenced and actually disappeared in diabetes of medium severity.

F. Romeo and A. Parrinello. *Acta vitaminol.* 8: 129, 1954.

GLYCINEMIA determinations were done on 16 patients with liver disease: (a) fasting; (b) after intravenous glycocoll. In both instances, blood glycine was higher in patients with liver disease than in normal subjects, and the glycine level seemed to be related to the severity of the disease.

E. Orlando. *Arch. "E. Maragliano" di Patol. e Clin.* 9: 685, 1954.

IN MAN, increasing the oral intake of vitamin B₁₂ from 0.5 to 50.0 µg. results in an increase in amount absorbed of only 1.0 µg. An intramural "intestinal B₁₂-acceptor" may exist which may be analogous to apoferritin in iron absorption.

G. B. J. Glass, L. J. Boyd, and L. Stephanson. *Proc. Soc. Exper. Biol. & Med.* 86: 522, 1954.

MAGNESIUM in the spleen and liver was shown by biopsy to be markedly reduced in cases of carcinoma and sarcoma. It is inferred that a generalized magnesium deficiency occurs in the presence of malignant growth, primarily in the bone system, but also, eventually, in the serum and blood corpuscles.

S. v. Nida and H. Baldauf. *Ärzt. Forsch.* 8: 368, 1954.

THE INCIDENCE of new dental caries in previously noncarious teeth treated with stannous chlorofluoride was reduced by about 85 per cent more than the reduction in the children who received the sodium fluoride treatment.

C. L. Howell and J. C. Muhler. *Science* 120: 316, 1954.

RECENT ADVANCES IN EXPERIMENTAL NUTRITION

STUDIES on experimental tumor production in the fruit fly showed that the incidence of tumors was higher in the presence of a high vitamin diet.

S. Mittler. *Science* 120: 314, 1954.

PANTOTHENIC acid deficiency reduced the production of antibodies (against *S. typhi* and *Br. melitensis*) in rats. It is claimed that the reduced antibody response was directly related to the pantothenic acid deficiency and not to the associated weight loss.

G. Giunchi, L. A. Scuro, F. Sorice, and A. Fidanza. *Riv. dell'Ist. Sieroterapico Ital.* 28: 281, 1953.

IN EXPERIMENTS with four strains of mice, vitamin B₁₂ and cobalt chloride had no additive effect on growth. Also, there was no beneficial effect on reproduction.

L. Mirone, and E. M. Wade. *Am. J. Physiol.* 175: 11, 1953.

DIHYDROCHOLESTEROL feeding in mice did not result in an increased rate of mobilization of liver cholesterol. Dietary soybean sterols did not accelerate the rate of decrease of plasma cholesterol levels in hypercholesterolemic rabbits.

W. T. Behrer and W. L. Anthony. *Proc. Soc. Exper. Biol. & Med.* 86: 589, 1954.

TOTAL PLASMA lipids of rats made fat-deficient were about two-thirds that of controls. The percentage distribution was not significantly different except for phospholipids, which remained essentially normal in absolute amount.

J. F. Mead and D. L. Fillerup. *Proc. Soc. Exper. Biol. & Med.* 86: 449, 1954.

Nutritional Quotes

Oral Deprivation

"In addition to the somatic factors of the disease, the psychologic effects of food deprivation in patients are frequently complicated by pain and the fears of the original disease, operative procedure and death. Yet it is believed that the absence of oral gratification in starvation may be psychologically important. This depends, to a large measure, on the normal or neurotic emphasis placed on oral gratification by the patient before his illness. In some patients with heart disease put on a rigorous diet there may develop a conflict between the fear of death and the anger associated with the food restriction. Their depression and apathy can only be overcome by providing more variety in foods and more oral gratification. The symptoms which are considered as possible indicators of psychologic changes accompanying food deprivation include the restlessness of postoperative patients, their irritability, and occasional unrealistic and infantile demands."

—*Nutrition Reviews* 12: 239, 1954.

Eating, Feeling, and Thinking

"From the review of the studies cited . . . it is clear that the relations among diet, emotions and behavior are complex, including food habits, symbolic values attached to food and eating, and motivated perception, as well as changes in physical fitness, mental alertness and personality which result from deficiencies of certain nutrients. The practical implications of these facts would lead one to expect more intensive research in this field than can be actually documented. The obstacles are as large as many of the problems are important. While reasonably satisfactory tools for a quantitative or at least semi-quantitative description of intelligence and personality are available for use in the laboratories and clinics of English-speaking countries, these instruments in the overwhelming majority are wholly inapplicable to native populations. However, progress in the scientific study of the gross and the more subtle impacts of diet on man's mind and behavior is one of the most intriguing developments in a comprehensive science of nutrition."

—*Nutrition Reviews* 12: 240, 1954.

Improved Calorimetry?

"The change in the composition of the body will always pose a problem for all caloric balance studies until such time as very small changes in the content of protein and fat can be detected in the intact organism.

Lacking such methods, the only alternatives are to make the study under such conditions that changes in body composition are minimized, or to make a complete balance which would require a measure of the carbon lost in the urine, feces and expired air, together with the caloric intake. With proper precautions, it would appear that experiments of this type might be carried out with the Kofranyi and Michaelis apparatus.

". . . There is as yet no exact indication of the accuracy that can be achieved with this apparatus. Should it be as accurate as it appears, then it will be of considerable aid in resolving some of the wide discrepancies currently existing in caloric allowances promulgated by different organizations. The establishment of reliable caloric requirements will assume increasing importance if a large-scale rationing program becomes necessary due to any future emergency."

—*Nutrition Reviews* 12: 197-198, 1954.

Anthropometry and Nutritional Status

"The composition of the human body is an important facet of the nutritional status (nutriture). While in the laboratory and the clinic the densitometric approach and the determination of fluid compartments are the methods of preference, in field work improved anthropometric methods will provide important new tools. Here further developments should proceed in several directions: (1) improvement of methods for the evaluation of man's physique from photographs, (2) estimation of anatomically defined tissue masses from external and radiologic measurements, and (3) development of equations for predicting total body fat from skinfolds, using the values obtained from density and total body water as criteria."

—*Nutrition Reviews* 12: 206, 1954.

Undernutrition and Atherosclerosis

"In these carefully recorded experiments [McMillan *et al.*] the effect of undernutrition on the atherosclerosis of cholesterol-fed rabbits has been examined in a number of ways. In every case it has been found that undernutrition was without significant effect on the development or the regression of aortic lesions. The serum cholesterol, both free and combined, was distinctly higher in the undernourished animals. In only one respect might the feeding of a calorically inadequate diet be considered protective against atherosclerosis. The atherosclerosis of the undernourished rabbits was no worse than that of the control rabbits despite higher cholesterol levels.

"The application of these experiments to human atherosclerosis is difficult, and caution is needed in their interpretation. There is some clinical evidence that in man atherosclerosis is accelerated in obesity and decreased under conditions of caloric insufficiency.

There are certain obvious differences in the experimental and clinical situation. In the rabbit experiments . . . fat and cholesterol intake were maintained at a high level in both the undernourished and control groups. Human subjects on calorically inadequate diets often have low intakes of these substances."

—*Nutrition Reviews* 12: 221, 1954.

Fructose, Insulin, and Ketosis

"Fructose administration has been recommended . . . for the treatment of diabetic ketosis. The work reported by Rosecan and Daughaday supports this advice, but as they point out 'insulin is necessary for the full anti-ketogenic effect.' That is, in the absence of insulin there was conversion of fructose to glucose, a subsequent rise in blood sugar and a markedly diminished tissue uptake of sugar.

"The evidence presented in this study supports the concept that carbohydrate in addition to insulin produces a more rapid decrease in ketosis than does insulin alone in the uncontrolled diabetic. This is due to an increased utilization of the sugar and is somewhat better when fructose rather than glucose is given."

—*Nutrition Reviews* 12: 228, 1954.

Not So Folic Acid

"Folic acid was so named because it was obtained from a foliage material, spinach, but it is no more characteristic of leafy materials than it is of liver or yeast. Liver and yeast have been more widely used than leafy materials in the isolation and characterization of the factors; hence, if source were to determine the name, 'hepatic acid' or 'cerevisic acid' would have been equally logical and suitable—perhaps one should say equally illogical and unsuitable."

—W. H. Peterson. *Nutrition Reviews* 12: 225, 1954.

Vitamin B₁₂ and Methyl Donors

"Various factors present in liver extract have been shown to influence methyl group synthesis. One of these factors is vitamin B₁₂. This substance reduces the experimental animal's requirement for methyl donors when homocystine is fed in place of methionine. In its presence growth performance is improved, less kidney damage results and mortality is less. Vitamin B₁₂ appears to exert no effect in the total absence of methyl donors. It seems to act by reducing the absolute dietary requirement for methyl groups."

—*Nutrition Reviews* 12: 218-219, 1954.

Aesthetics at Autopsy

"Some while before retirement from my chair I had been much struck with the variations in colour of the fat of Australians. In some bodies this was of a beautiful buff yellow or chrome colour, so rich that one felt quite a regret that its owner never knew what was under his skin. The idea was probably unfounded, but one thought of those with soft fat of a dingy white colour as having particularly relished and fed on the flesh of swine, and of those with the rich yellow fat as being essentially beef-eaters. In spite of so much mutton being eaten, one did not see at autopsies a nearly pure white, firm type of human flesh. . . .

"The subcutaneous fat of newly born babies and of infants is very pale and arranged in little lobules. . . . I have no notes of when the fat of children may become coloured. . . .

"When people who have once been fat become greatly emaciated, one finds in some cases in the subcutaneous tissues richly coloured shrunken lobules. Though the fat has been absorbed, the carotenoids associated with it have been left behind and concentrated."

—J. B. Cleland. *The Medical Journal of Australia* 41: 588, 1954.

Hypothetical Seduction

"The major pleasure of scientific research is in the creation of successful working hypotheses, but the affection their authors tend to conceive for such creations can be dangerous: like Galatea, the hypothesis comes to have a life of its own."

—R. B. Fisher in *Protein Metabolism*, John Wiley & Sons, New York, 1954, p. 187.

Reviews of Recent Books

Food for Life, edited by Ralph W. Gerard, The University of Chicago Press, Chicago, 1952, pp. 306, \$4.75.

This presentation of the science of nutrition is especially excellent because it includes the necessary background of physiology and biochemistry, making for a complete story rather than the usual type of fragmentary picture.

Not a nutritional handbook, this is an exposition of the scientific bases of nutrition. The text is written and beautifully illustrated with dramatic cartoons and graphs, so that the various aspects of nutrition such as digestion, metabolism, control of metabolism by enzymes and hormones, bioenergetics, and the fundamental concepts of human nutrition may be understood by the lay reader. Throughout the text the authors have compared the complex human engine with the mechanical engine. The analogy cannot hold in many instances, but that fact alone permits the reader to appreciate the wonders of the animal body and the relationship of physiological and biochemical function to nutrition. This is further emphasized by demonstrating what the body needs, what foods supply these needs, and how the body converts these foods into its own substance and into energy for life's activities.

The introductory chapter, *The Basic Questions of Nutrition*, poses for the lay reader those questions which have guided research workers in their investigative activities along the bypaths of nutrition. The succeeding chapters attempt to answer these questions in the light of modern knowledge. The nutrient materials of foods are discussed in detail. This is followed by a discussion of the methods by which the human body prepares the ingested food for absorption by the cell and to take part in the multiple metabolic activities of the cell. Of course the authors, rightly enough, do not neglect the role of food selection, food preparation, and food supply in the overall problem of nutrition. The intermediate metabolic processes inside the cell are discussed next. Of particular importance is the introduction of the basic concept of the *Metabolic Pool*. The chapter is concluded by a discussion of the interrelation of carbohydrate, fat, and protein metabolism.

The two chapters which follow deal with the regulation of cell metabolism. The role of enzymes and hormones in the control of biochemical reactions is discussed in detail. The dietary sources of coenzymes and the relationship of malnutrition, undernutrition,

and cellular metabolism are presented. In this way the authors develop the idea of the dietary deficiency and the metabolic block. Finally, the level of regulation reaches the steering stage. The body has been set in motion by energetic and enzyme mechanisms, and now the hormones are discussed as the physiological forces which tend to keep the cell along the proper metabolic pathway.

Finally, the authors consider the purpose of nutrition: to provide energy for life processes, and to provide raw materials for tissue growth and tissue repair. Along with these fundamental aspects they present information on the requirements for energy, the expenditure of energy, and the methods for measurement of physiological energy exchange during normal physiological activities. Here again the authors discuss the role of hormones and the endocrine glands in controlling biochemical equilibrium during periods of growth or of the steady state.

The closing chapters of the book discuss nutritional problems confronting man. The chapter on the food of man discusses the evolution of the human diet. The final chapter, *The Improvement of Human Nutrition*, discusses the present trends in human nutrition—how our diet compares with the known recommended requirements. It also considers how our diet will relate to our physiological well-being in our later years, that is, over 65 years of age. The book closes with a realistic discussion of food problems for the future and the universal need for nutritional educational programs throughout the world.

This book with its clear exposition and superb diagrams should be found in every physician's bookcase for his own use and his patients'.

CARL ALPER

General Biochemistry by W. H. Peterson and Frank M. Strong, Prentice-Hall, Inc., New York, 1953, pp. 469, \$8.65.

This textbook is a good introduction to the subject of biochemistry for the student of nutrition. Although the text is brief, the subject matter covers the whole field of biochemistry, encompassing mammalian, plant, and microbiological biochemistry. The presentation is assisted by a text replete with tables and figures. In addition, the authors provide material for future study by incorporating at the end of each chapter a set of review questions and references to other textbooks, monographs, review articles, and current periodicals.

Interestingly enough, the authors take note of the primary role of water in metabolism and structure by discussing it first in their consideration of the composition of tissues. A substance which comprises 70 per cent of the lean body mass deserves this emphasis.

From the point of view of nutrition, the chapter on acidity contains an excellent discussion of acid- and base-forming foods. The chapter also contains a résumé of the method of analysis for a given constituent in biological materials.

The chapter on mineral composition contains a very useful table of the specific organic compounds of mineral elements in plant and animal materials and some excellent pictures of mineral deficiencies in plants and animals.

The section on enzymes contains a very interesting table of enzyme classification in which many important biochemical reactions are discussed, indicating the substrate, product formed, and the necessary cofactors. The discussion on coenzymes is up to date and contains information on lipoic acid, lipothiamide pyrophosphate, and coenzyme A.

The chapters on animal metabolism, plant metabolism, and metabolism of micro-organisms are brief but exceedingly well done. The diagrams of the metabolic cycles indicate the required cofactors and the equilibrium of each individual reaction where known. The authors discuss not only the metabolic cycles but also the fundamental biochemical and bioenergetic significance of each set of reactions. Finally, they discuss the overall net effect of each metabolic cycle.

The section on metabolism is followed by a chapter on Biological Energetics which is not usually included in an elementary textbook. The authors discuss the relationship of bioenergetics to muscle contraction, the generation of high energy phosphate bonds in metabolism, and the determination of energy exchange in biological systems from calculations of heats of combustion of essential metabolites.

The four tables contained in the appendix are of special value to all nutritionists. The tables describe the composition and energy value of foods.

CARL ALPER

The Year Book of Endocrinology, edited by G. S. Gordon, M.D., Ph.D., The Year Book Publishers Inc., Chicago, 1954, pp. 390, \$6.00.

In this volume can be found many of the important contributions from foreign and domestic journals dealing with endocrine and metabolic disorders. The abstracts prepared from the original articles are quite thorough, providing the essential details of studies performed or treatments employed. The usefulness of the book is enhanced by the inclusion of the actual dosages of the preparations, making it unnecessary to refer to the original paper in most instances. In addition to providing a review of the endocrine literature from 1953, there are running commentaries on the contributions prepared by the editor, presenting his

authoritative opinions upon the subjects under discussion. This feature aids in the crystallization of the reader's thoughts on a given topic by presenting data from older literature or by comparing the principles outlined in the abstract with those of other workers in the field. Preceding each section devoted to a specific endocrine organ, the editor has discussed in general terms the most recent advances relating to the gland, its functions, and metabolic interrelationships. An additional section on the endocrine treatment of neoplastic diseases is included. This book will serve as an excellent reference source for practitioners and students of endocrinology, providing a well-integrated coverage of the recent literature in this field.

C. R. SHUMAN

Symposium on Protein Metabolism (*Nutrition Symposium Series No. 8*), edited by E. W. McHenry, National Vitamin Foundation, Inc., New York, 1954, pp. 103, \$1.50.

This is a report of seven of the papers given at the Nutrition Foundation Symposium on October 30, 1953. Papers reported include: The Relation of Vitamin B₆ and Riboflavin to Protein Metabolism; The Interrelationship Between Vitamin B₆, Steroids, and Proteins; Role of the Vitamins in Antibody Production; Effects of Growth Hormone Preparations on Protein Metabolism; The Amino Acid Requirements of Man; Factors Influencing Amino Acid Utilization in Tissue Protein Synthesis; and Amino Acids and Protein in Therapy.

For the subjects covered, this is an excellent little review of vitamins and protein metabolism. The articles are concise, the original work is presented clearly, and the references in a few of the papers are comparable to those of standard review articles.

PAUL GYÖRGY

Colloque sur les Acides Aminés by A. Vannotti, E. J. Bigwood, G. Frontali, M. Polonovski, and C. Remington. S. Karger, Basel, 1954, pp. 333, Sw. fr. 25.

This is a report of a symposium on amino acids held in Lausanne April 16 to 19, 1953.

The papers were presented in three parts: (1) *Methods*. This included discussions of columns of ion exchangers, and a new microbiological test for amino acids. (2) *Physiopathological problems*. This included papers on absorption and intermediate metabolism, amino acids in the synthesis and structure of proteins, and aminoacidemia and aminoaciduria. (3) *Clinical and therapeutic problems*. This included hydrolysates in the treatment of prematures and full term infants, pancreatic fibrosis, pulmonary tuberculosis, ulcers, and kwashiorkor.

The book is a good review of amino acids in these three fields, although some of the articles are only summaries. The references are valuable.

PAUL GYÖRGY

Abstracts of Current Literature

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INFANT FEEDING

It is not surprising to learn that breast feeding is recommended very strongly as a means of overcoming some of the psychological difficulties associated with infant feeding. It is interesting to note that nutritional anemia in infants was directly attributable to feeding disturbances in nonbreastfed infants. Thus, not only does human milk provide a superior type of pabulum nutritionally, but it also evokes a desirable emotional reaction of the baby to his environment.

Psychologic Aspects of Infant Feeding. J. B. Richmond and G. H. Pollock. *J. Am. Dietet. A.* 29: 656, 1953.

"The early feeding experience of the infant constitutes his major contact with the outside world. His physiologic comfort, or lack of it, depends to a great extent on how and when he is fed."

So state the authors of this article which emphasizes the importance of details of the feeding process during infancy in shaping the emotional pattern of the child. Pediatricians and psychiatrists have come to appreciate increasingly that details, no matter how small, may have far-reaching effects upon the physical comfort and emotional development of the individual. One of the best ways to provide a comfortable feeding experience for the infant is the encouragement of breast feeding. From a nutritional point of view, breast milk is a biologically adequate, species-specific

food, and is therefore preferable. With breast feeding go such intangibles as the picking up, fondling, and physical closeness which the baby feels. It may be more unwholesome for mother and baby, however, to insist on breast feeding by a mother who is unaccepting psychologically than to assist her in adapting artificial feeding. Intelligent use of self-regulatory intervals in infant feeding has potentialities for desirable emotional reaction of the baby to his parents and ultimately to other adults and his environment.

Social and emotional disturbances in the home are possible causes of infantile disorders in gastrointestinal function. Nutritional anemia has been observed in 12 infants who manifested one type of reaction. All had refused to accept semisolid foods, and the complete milk diet low in iron resulted in profound anemia. This anemia set in during the latter half of infancy or early childhood; it responded well to therapy during hospitalization with concomitant clarification of the patients' problems with parents. None of the patients had been successfully breastfed. In all cases, emotional problems manifested by feeding disturbances were present. Social and economic difficulties experienced by the parents in some instances served to create or intensify disturbed relationships between parents and infant. The authors conclude: "Respect for individual feeding patterns, both quantitatively and qualitatively, is significant in helping to assure physiologic comfort for the infant and thus enhancing healthy emotional development."—J. SMITH

The nutritional experience of "healthy, normal" children is a matter of interest and importance. Information such as described below helps to set the pattern of our recommended policies.

Nutritional Intake of Children. I. Calories, Carbohydrate, Fat and Protein. V. A. Beal. *J. Nutrition* 50: 223, 1953.

For the past quarter century, the Child Research Council has been studying the physical, physiological, and psychological growth and development of a group of children in the Denver, Col. area. These children, who come from "upper middle class" families, are primarily of Northern European extraction. They are enrolled in the study early in the prenatal period and are followed throughout the period of growth into adulthood.

Data have been presented from 604 nutrition histories on 46 children in the first five years of life. Calories, carbohydrate, fat, and protein intakes, referred to age and body weight, have been computed in terms of qualities and maximum and minimum intakes. Total intakes of calories, carbohydrate, and fat increase throughout the period from birth to five years. Intake of protein, however, reaches a plateau between 18 months and three years, reflecting the capricious eating habits of the preschool child. The median calorie intake is close to the recommended dietary allowance of the National Research Council; the median protein intake is above the recommended dietary allowance in the first two years and thereafter is similar to the allowance. Intake of protein per kilogram of body weight shows a consistent decrease in this age period. The descending curve of intake of calories, carbohydrate and fat per kilogram of body weight is interrupted by a temporary rise in the second year.—B. SURE

The feeding of premature infants calls forth all our nutritional knowledge. Breast milk is recognized as being superior to cow's milk. However, when artificial feeding is necessary there are good reasons for considering the difficult role of the premature kidney in handling a concentrated, high protein intake. These important subjects are discussed in the following papers.

The Feeding of Premature Infants. S. Z. Levine and M. Dann. *Courrier du Cent. internat. de Pen-ance* 3: 429, 1953.

Based on an extensive experience in the feeding of premature infants at the New York Hospital, the authors recommend the following feeding schedules in the hospital management of premature babies: for premature infants weighing less than 1750 Gm.—half-skimmed cow's milk mixtures, high in protein and low in fat; for premature infants weighing more than 1750 Gm. but unable to suckle the breast directly

—evaporated or boiled whole cow's milk mixtures. For premature infants strong enough to nurse, breast feeding is recommended.

According to the authors, cow's milk when properly modified is superior to human milk in promoting weight gains in premature infants under controlled conditions of cleanliness, temperature, and good nursing care in a hospital. Partially skimmed-milk formulas seemed to be most suitable. This, however, does not apply to the larger prematurely born or full-term infants who are strong enough to nurse directly. For many reasons, breast milk remains the food of choice. However, breast milk obtained directly is entirely different from human milk collected, pooled, heated, frozen, warmed before feedings, and fed by bottle. This processing, even of human milk, results in as artificial a feeding as cow's milk similarly processed.—S. O. WAIFE

The Effect of Added Carbohydrate on Growth, Nitrogen Retention, and Renal Water Excretion in Premature Infants. P. L. Calcagno and M. I. Rubin. *Pediatrics* 13: 193, 1954.

These authors were interested in the influence of added carbohydrate to milk feedings on renal solute and water excretion in premature infants. Using the balance study technique, two groups of premature infants with similar fluid intakes of 150 cc./Kg. have been studied. Group I (4 infants), weighing between 1225–1780 Gm., constituted the isocaloric group and received 125 cal./Kg./day. The formulas varied primarily in their carbohydrate and protein content and were designated "concentrated cow's milk" and "added carbohydrate." In the "concentrated cow's milk" formula, 21 and 26 per cent of the total calories were present as protein and carbohydrate, respectively, resulting in 7.4 Gm. of protein/Kg./day. The protein in the "added carbohydrate" formula constituted 16 per cent of the total calories, or 6 Gm./Kg./day; the carbohydrate in the "added carbohydrate formula" constituted 42 per cent of the total calories. Group II (5 infants), weighing between 1225–2120 Gm., constituted the "isonitrogenous group." The protein, carbohydrate, and fat distribution of calories in 4 diets used on this group of infants ranged from 16 to 25, 25 to 43, and 39 to 53 per cent, respectively; this made it possible to determine the effect of added carbohydrate on nitrogen retention and osmolar (solute) excretion while the infants were receiving isonitrogenous feedings at different levels of protein intake.

The high protein content in all formulas was intentional and made possible the determination of the effect of osmotic loads on renal water losses.

The authors observed that nitrogen retention was greater both when the nitrogen intake was greater and when the total calories as carbohydrates were greater. "Added carbohydrate" caused a decrease in blood urea nitrogen (BUN) and a decreased urinary excre-

tion of urea, sodium, and potassium, with a decrease in total osmolar load. The greater urinary concentration associated with the high protein diet is a reflection of the smaller urine volume per milliosmol of solute excreted. Added carbohydrate which is completely metabolized does not contribute to renal excretory load and results in a decreased demand for obligatory water excretion.

Therefore, in the presence of incompletely developed renal functions, a diet offering a smaller load for renal excretion is desirable.

The "added carbohydrate" in group II (isonitrogenous) resulted in a greater weight gain than the "noncarbohydrate" diet because of a higher caloric content; however, in Group I (isocaloric group), the "added carbohydrate" formula also resulted in a greater weight gain, although the protein intake was reduced 19 per cent.

As stated by the authors, these results supply added evidence to support the data of Pratt and Snyderman that a decrease in protein intake results in a diminution in the obligatory water expenditure, at a given renal concentrating capacity. These data supply added evidence of the immaturity of renal functions which has been observed in premature and in full-term infants during the first weeks of life by Rubin, Barnett, McCance, and others. Concentrated feedings without respect for water needs or the sparing effects of carbohydrate are undesirable.—J. N. ETTELDORF

Chromatographic analysis of milk obtained from human donors reveals the presence of essential and nonessential amino acids in quantities larger than previously reported. Although human milk contains less protein than cow's milk, it is possible that the distribution of the amino acid constituents is more important than the quantitative aspects. Along these lines is the report of the effect of heat processing (autoclaving, etc.) on milk as a nutrient source.

Amino Acid Composition of Human Milk. P. Soupart, S. Moore, and E. J. Bigwood. *J. Biol. Chem.* 206: 699, 1954.

Chromatographic analyses were performed on two mixed samples of human milk, one representing pooled milk from 20 donors in the urban area of Brussels obtained in the middle of winter, and the other from 40 donors from the same area collected at the end of the winter series. The amino acid composition was determined chromatographically and the results showed that glycine, alanine, proline and glutamic and aspartic acid are present in larger amounts than previously reported. As is true of most foods, the four nutritionally important amino acids present in the smallest amounts are cystine, methionine, tryptophane, and histidine, which average 23, 20, 19, and 21 mg. per 100 ml. of milk, respectively. The analyses accounted for 88 per cent of the total nitrogen in terms of amino acids and ammonia, much of the ammonia

coming from the urea in human milk. About 5 per cent of the total nitrogen comes from unknown constituents and minor components such as creatine, creatinine, uric acid, and choline.—M. K. HORWITT

Heat Processing and the Nutritive Value of Milk and its Products. L. J. Schroeder, M. Iacobellis, and A. H. Smith. *J. Nutrition* 49: 549, 1953.

While it is generally recognized that proteins subjected to heat are not as well utilized for growth and do not support favorable nitrogen balances as do unheated proteins, no deleterious effects were found in processing milk and its products under the experimental conditions used in this study. Tests on adult dogs have shown that autoclaving whole raw milk at 10 or 15 pounds' pressure for 15 or 30 minutes had no detrimental effect on the proteins as measured by digestibility, biological value, or nutritive index. It was also found that the digestibility and biological value of milk proteins do not change if milk is kept in frozen storage for 5 months. It was observed that, under the experimental conditions employed, commercial processing as is used in the production of evaporated milk and milk powder does not decrease the nutritive value of the protein constituents.—B. SURE

Infants unable to consume milk because of allergy or metabolic disturbances have been fed a mineral-enriched meat formula. The metabolic balance studies performed on these patients have disclosed a positive balance for nitrogen, calcium, and phosphorus. This interesting preparation may also be found useful in the management of nutritional problems outside the field of pediatrics.

Mineral-Enriched Meats for Diets of Infants Requiring a Milk Substitute. M. R. Ziegler. *J. Am. Dietet. A.* 29: 661, 1953.

Allergy to milk proteins and the metabolic disturbance known as galactosemia are two conditions in which milk is not indicated for infants. A mineral-enriched formula derived from strained meat is described which, when fed to young rats, resulted in weight gains and carcass analyses similar to those of milk-fed control rats.

The mineral-enriched meat formula has proved invaluable for six patients with allergy to milk proteins, one patient with galactosemia, two epileptic patients, two patients with familial hypoglycemia, three with lipoid nephrosis, one child who could not fabricate serum proteins normally, and one patient each with familial periodic paralysis, residual partial paralysis, progressive muscular dystrophy, and pituitary dwarfism.

Results of nitrogen, calcium, and phosphorus balance studies on six subjects are presented in the paper. In balance periods varying from 4 to 11.5 days in length, there were definitely positive mineral balances.

A case history describes a two-and-one-half-month-old boy who had a history of diarrhea since birth. He weighed 3859 Gm. and looked acutely ill. The meat feeding resulted in weight increase to 8850 Gm. at five months and permitted his discharge from the hospital. Another case study is given for an infant with galactosemia. The author found the mineral-enriched meat superior to milk for these two children and believes this products shows promise for certain cases with special dietary problems.—J. SMITH

The following articles are recommended for those who are interested in the historical and exotic aspects of infant feeding.

A History of Infant Feeding—Part I. I. G. Wickes. *Arch. Dis. Child.* 28: 151, 1953.

In an abbreviated but well-documented manner, the history of infant feeding among primitive peoples, as described in ancient works by Renaissance writers, is presented.

The various methods of breast feeding as practiced by early primitive tribes and during early Greek and Egyptian civilization are described. The duration of suckling, which in certain instances continued beyond four years of age, as well the odd methods of testing the milk, are described.

Because of scanty available information, little was stated concerning supplemental and complemental feeding, although it is evident that such occasionally was the case. It is apparent that the problem of continuing the flow of breast milk has been a long-standing one; interesting and amusing concoctions which were used are described in this article.

The article is recommended as a brief, enjoyable, and informative statement concerning breast feeding and its problems during these periods of world history.—J. N. ETTELDORF

The Chemical Composition of New Hebridean Human Milk. F. E. Peters. *Brit. J. Nutrition* 7: 208, 1953.

The peoples of the New Hebrides, like those of most Pacific areas, do not wean their infants until a relatively late age. It is common to see children of 18–24 months still suckling, and the normal procedure is to wean the child between 12 and 24 months of age, unless another pregnancy intervenes, when the child is weaned immediately. It was decided to determine the composition of New Hebridean native breast milk and also to try to determine whether there were any marked differences between the proportions of milk constituents of European and Melanesian woman and whether there were any changes in the constituents during the later lactation periods.

Fifty-one samples of human milk from Melanesian natives of the New Hebrides and seven samples of European milk from Canberra were analyzed for lac-

tose, fat, protein, ash, calcium, and phosphorus. It would appear that Melanesian human milk may have lower lactose and calcium content than European human milk. There was a slight decline in the non-fatty constituents over the lactation period of 2–24 months.

Before any definite conclusions can be made as to the relative chemical composition of Melanesian and European human milk a much greater number of samples, especially European, should be analyzed.

B. SURE

BIFIDUS FACTOR

The intestinal bacterial flora of breastfed infants contains a predominance of Lactobacillus bifidus. The investigations of György and associates have revealed the presence of a factor in human milk which supports the growth of a variant of L. bifidus. In most recent studies, this factor appears to be a mucopolysaccharide and may be closely related to Castle's intrinsic factor and to the blood group hemagglutinins. The initial report on this growth substance deals with the requirements of L. bifidus for growth. It is not destroyed by autoclaving but is destroyed by ashing.

Bifidus Factor. I. A Variant of Lactobacillus bifidus Requiring a Special Growth Factor. P. György, R. F. Norris, and C. S. Rose. *Arch. Biochem. & Biophys.* 48: 193, 1954.

The intestinal flora of the normal breastfed infant is characterized by the prevalence of *Lactobacillus bifidus* in contrast to the mixed flora of infants fed cow's milk formulas.

The specific variable of *L. bifidus* has been propagated and designated *L. bifidus* var. *Penn.*, which showed little if any growth in the regular medium, but which could be maintained through regular transfer of the basic medium supplemented with 2 per cent of skimmed milk. A large number of organic compounds, including microbiological growth factors, as well as many carbohydrates, and several vegetable extracts, were tested for growth-promoting activities and found to be ineffective as "bifidus factor." The bifidus factor in human milk is not destroyed or altered in its activity by autoclaving.—M. K. HORWITT

The intestinal bacterial flora of infants fed cow's milk contains a mixed population. It is interesting that cow's milk has only one-fiftieth of the bifidus factor activity of human milk. A number of other human secretions in addition to milk are shown to be active.

Bifidus Factor. II. Its Occurrence in Milk from Different Species and in Other Natural Products.

P. György, R. Kuhn, C. S. Rose, and F. Zilliken. *Arch. Biochem. & Biophys.* 48: 202, 1954.

The activity of human milk in the growth of *Lactobacillus bifidus* var. *Penn.* was compared with that of other species for bifidus factor. The milk of ruminants (cows, ewes, and goats) showed only very slight activity. Somewhat higher activity was found in the milk of cat, monkey, dog, donkey, rabbit, mare, and sow. The average relative activity was highest in human colostrum, closely followed by rat colostrum, then by human milk, rat milk, and cow colostrum. High concentrations of the bifidus growth factor were found in the saliva, semen, amniotic fluid, meconium, and tears of man. Ammonium salts and N-acetylglucosamine as well as N-acetylgalactosamine, especially the ammonium salts, in high concentration, were active, probably as precursors of the growth factor. Furthermore, hog gastrin mucin was shown to have a high titer for bifidus factor.—M. K. HORWITT

The growth factor present in human milk could be separated into a dialyzable and a nondialyzable fraction. However, the growth-promoting activity present in the blood group substances is nondialyzable. It appears that the L. bifidus growth factor is not in a uniform state in natural secretions.

Bifidus Factor. III. The Rate of Dialysis. P. György, J. R. E. Hoover, R. Kuhn, and C. S. Rose. *Arch. Biochem. & Biophys.* 48: 209, 1954.

Samples of skimmed fresh human milk and colostrum were dialyzed against distilled water and the microbiological activities of the inside and outside solutions determined for the bifidus factor. The active components of human milk and colostrum are apparently of different molecular size, the dialysis being slower for the factor in colostrum. Approximately 40–75 per cent of the overall activity could be obtained in the dialyzable fraction, and the nondialyzable fraction contained 25–60 per cent. By comparing the rates of dialyses of the bifidus factor with that of glucose, lactose, and melezitose, it was determined that the latter dialyze more rapidly than the bifidus-active factors.—M. K. HORWITT

Bifidus Factor. IV. Preparations Obtained from Human Milk. A. Gauhe, P. György, J. R. E. Hoover, R. Kuhn, C. S. Rose, H. W. Ruelius, and F. Zilliken. *Arch. Biochem. & Biophys.* 48: 214, 1954.

The growth factors in human milk for *Lactobacillus bifidus* var. *Penn.* consist of a group of N-acetylglucosamine-containing oligo- and polysaccharides. Using the microbiological test with *L. bifidus* var. *Penn.*, large amounts of human milk have been processed for the isolation and characterization of these factors.

Cream, proteins, and salts can be removed from human milk by freezing out the cream, precipitating with barium hydroxide and zinc sulfate, and adsorp-

tion on amberlite resins, respectively. Hydrolysis of the lactose-free active concentrates gave acetic acid and four sugars, D-glucosamine, L-fucose, D-glucose, and D-galactose. By chromatography on charcoal and on paper, at least four different active components were found, all of which contained N-acetylglucosamine units.—M. K. HORWITT

PROTEIN NUTRITION

The rapid turnover of enzymes in the pancreas makes great demands on the biosynthetic mechanism for protein synthesis in this organ. According to Mirsky, the total cellular protein within the pancreas does not change during the secretion and synthesis of enzymes, which would indicate that the production of protein by these cells must be as rapid as its secretion. Therefore, in the presence of protein deficiency, one would anticipate functional and morphological alterations of the pancreatic acini. This has been studied in rats.

Relation of Dietary Protein Levels to Pancreatic Damage in the Rat. M. Wachstein and E. Meisel. *Proc. Soc. Exper. Biol. & Med.* 85: 314, 1954.

Rats maintained on a protein-free diet at the end of 40 to 45 days showed marked atrophy of the pancreatic acini. The addition of 2 per cent casein was not protective. In animals receiving the addition of 4 per cent casein, the pancreatic lesions were considerably milder. If 7.5 per cent casein was added, the pancreas appeared almost normal. The addition of 1 per cent methionine to the basic diet gave about the same protective effect as did 4 per cent casein.—L. W. KINSELL

Pancreatic insufficiency will result in excessive loss of fecal fat and nitrogen, which may be reversed by the administration of certain pancreatic ferments. Tween 80® or Aureomycin® failed to reduce the excessive fecal nitrogen losses.

Studies on the Therapy of Pancreatic Insufficiency. W. A. Clay, D. W. Frank, and V. W. Logan. *Gastroenterology* 26: 198, 1954.

The authors attempted to assess the influence of a number of factors in metabolic experiments on dogs with creatorrhea and steatorrhea following pancreatic duct ligation.

One month after operation they were placed in metabolism cages and fed a synthetic diet, while balance studies were carried out.

The following substances were investigated: enteric-coated pancreatin granules, Viokase®, Papain, Tween 80®, and Aureomycin®.

Enteric-coated pancreatin and Viokase administered at 21 per cent of the nitrogen intake had a marked and equal effect in reducing the excessive fecal nitro-

gen and fat loss. Papain when fed at a level of 2 per cent of the dietary nitrogen, resulted in considerable improvement in the steatorrhea and sometimes in the steatorrhea. Papain was not as effective as pancreatin or Viokase. Tween-80 or aureomycin under the conditions of this study did not reduce the fecal loss of nitrogen or fat.—S. H. LORBER

It has been previously demonstrated that certain proteins and amino acids may increase the output of cholate in the bile, which has led to the following investigation of the effect of casein on the fecal excretion of fat. It is conceivable that the reduced fecal fat excretion on high protein diets is the result of an increased pancreatic lipase excretion which has been observed during casein feeding of rats.

Nature of the Decrease in Fecal Fat Resulting from the Feeding of Protein. D. F. Magee, K. S. Kim, and A. C. Ivy. *Am. J. Physiol.* 177: 285, 1954.

When high casein diets are used, the fecal fat excretion is less than on isocaloric high carbohydrate diets (glucose or sucrose as extra carbohydrate source). Gelatin is just as effective as casein. The author concludes that reduction in fecal fat on protein feeding is not related to changes in bile acid output.—M. J. OPPENHEIMER

During starvation, considerably more body protein nitrogen is catabolized in the adult than in the newborn infant. This is an interesting observation which is deserving of further investigation.

Protein Catabolism and Oxygen Consumption during Starvation in Infants, Young Adults and Old Men. R. A. McCance, and W. B. Strangeways. *Brit. J. Nutrition* 8: 21, 1954.

Normal newborn male infants and young and old men were allowed no food and a restricted fluid intake for 48 to 72 hours. Urine and blood were collected over this time and the basal metabolic rates were measured. The basal metabolic rates of the three groups averaged 50, 26, and 21 cal./Kg./24 hours, respectively, during starvation.

The body nitrogen catabolized on these days averaged 0.075 Gm./Kg./24 hours in the infants, 0.17 in the young adults and 0.12 in the old men. It follows that starving young adults and old people derived about 19 per cent of their calories from protein, but infants, during the first 48 hours of their lives, only 4 per cent.—B. SURE

The following two papers, emerging from studies conducted in Africa and dealing with malnutrition in adults, are of great interest and should be read in their entirety. This is an example of a very thorough study conducted in a group of patients suffering from a condition which is relatively unusual in more eco-

nomically sound regions of the world; namely, severe deficiency of dietary protein. A remarkable rate of nitrogen retention has been observed in these subjects during refeeding programs.

Malnutrition in African Adults. 1. Serum Proteins, Cholinesterase, and Protein-bound Lipid. M. W. Stanier and E. G. Holmes. *Brit. J. Nutrition* 8: 155, 1954.

The type of malnutrition most commonly seen in East Africa appears to be due to a deficiency of dietary protein. It is not "undernutrition," i.e., deficiency of intake of calories and all dietary constituents. Nor do the symptoms suggest a deficiency of any of the known vitamins. That the malnutrition is due to inadequate protein intake is suggested both by a consideration of the staple foods and dietary habits of the population and also by the symptoms of adult patients admitted to hospital with a diagnosis of malnutrition.

Adult men suffering from protein deficiency malnutrition were treated with a high calorie, high protein diet. During treatment their red cell count, serum proteins, serum pseudo-cholinesterase and protein-bound lipid were studied. At the beginning of treatment, whether or not the patients had clinical evidence of liver damage, they had low levels of serum albumin and raised levels of globulin. The "fraction X," a component with the mobility of γ -globulin but estimated chemically as β -globulin, was on an average higher in patients than in normal Africans or Europeans. During treatment with a high calorie, high protein diet, the serum albumin (and red cell count) rose. The changes in globulin were not consistent, but the fluctuations occurred mainly in the component measured as γ -globulin by electrophoresis and as β -globulin by the chemical method.

Serum pseudo-cholinesterase was low in such patients and rose as the serum albumin increased. There was less lipid in the lipoproteins in persons with malnutrition than in normal subjects.—B. SURE

Malnutrition in African Adults. 2. Protein Storage. E. G. Holmes, E. R. Jones, and M. W. Stanier. *Brit. J. Nutrition* 8: 173, 1954.

In 1948, the authors of this investigation had occasion to undertake a series of nitrogen balance experiments on African patients in Mulago hospital, Kampala, Uganda, with a view to assessing their state of nutrition with respect to protein. Some had been admitted to hospital suffering from severe hookworm anemia, others with enlargement of the liver and spleen sufficient to bring them into hospital. Others bore the diagnosis simply of "malnutrition." They all gave a history, extending over years, of a diet grossly deficient in proteins, and from which animal protein was almost absent. Malnutrition of the type encountered here differs from that seen in Europe and America, in that very serious protein

deficiency may accompany a diet of reasonable calorie value. Bayliss's dictum "Take care of the calories, and the protein will take care of itself" is emphatically not true in this part of Africa. This is because the common carbohydrate staples, sweet potato, cassava, and plantain, contain 2 per cent or less of protein.

The nitrogen balance of Africans who have lived for a long time on diets very deficient in protein has been observed for long periods. On a diet high in protein and calories they retained nitrogen at rates of up to 10 Gm./day continuously for months. The proportion of nitrogen lost in the feces was considerably greater than that of control subjects. The retention of nitrogen was markedly diminished by cortisone.—B. SURE

The value of any protein as a nutritional substance depends primarily upon its amino acid composition and upon the availability of these amino acids during the processes of digestion and absorption. For this reason, detailed studies of the amino acid content of protein-containing foods will continue to engage the interest of biochemists and nutritionists. In the following study it has been shown that nitrogen fertilization markedly increased the protein content of corn, not only in the zein fraction, but also in other proteins.

The Amino Acid and Protein Content of Corn as Related to Variety and Nitrogen Fertilization. H. E. Sauberlich, Wan-Yuin Chang, and W. D. Salmon. *J. Nutrition* 51: 241, 1953.

A series of 19 samples of grain corn was analyzed for protein and 18 amino acids. The results revealed that the nitrogen fertilization employed and the variety selected may influence considerably the protein and amino acid contents of the corn kernel. The protein content of the samples ranged from 6.8 to 12.0 per cent. The amount of all the amino acids increased with an increase in the protein content of the corn. However, there were considerable differences in the rate of increase among the individual amino acids.

The results indicated that with the higher protein corn samples a greater proportion of the protein was zein as compared to the low-protein samples, which would indicate that, from the viewpoint of nonruminant nutrition, the quality of the protein in the high-protein corn would be actually inferior to that of the low-protein corn.

Nitrogen fertilization increased the protein and amino acid content of corn significantly, with the increase apparently in the zein fraction. However, the other proteins were also increased with an increased protein content of corn, as was evidenced by the percentage of greater amounts of lysine and tryptophane.—B. SURE

In animal feeding experiments it has been found that the high protein corn samples were superior to the low protein samples in growth-promoting effects. Supplementation of the corn diets with soybean meal produced very satisfactory growth responses.

The Comparative Nutritional Value of Corn of High and Low Protein Content for Growth in the Rat and Chick. H. E. Sauberlich, Wan-Yuin Chang, and W. D. Salmon. *J. Nutrition* 51: 623, 1953.

A series of corn samples, ranging in protein content from 6.8 per cent to 13.6 per cent was employed in feeding experiments with rats and chicks. The low-protein varieties (range of 6.8 to 9.1 per cent) were markedly increased in their protein content (9.5 to 13.6 per cent) by increased rates of nitrogen fertilization.

The high-protein samples were superior to the low-protein samples when fed on the basis of equal proportions of corn grain in the diet. The low-protein corn was found to be deficient in at least the following amino acids: lysine, tryptophane, isoleucine, threonine, and valine. In contrast, the high-protein corn was deficient only in lysine and tryptophane, although not as severely deficient as the low-protein corn. However, when the corn was fed on the basis of equal protein content in the diet, the high-protein corn was somewhat inferior to the low-protein corn which contained a greater portion of zein in the protein.

Studies on the supplementation of corn diets with various natural protein materials indicated that soybean meal is the most satisfactory of those tested. The protein supplements were most effective when added to the high-protein corn diets.—B. SURE

The content of certain amino acids of the muscle meat and organs of beef and other food animals has been determined by microbiological methods. These studies, together with similar data obtained by other methods, involving the nutritional aspects of certain vegetable proteins, are presented in the following papers. These findings should be of considerable interest to nutritionists.

The Alanine, Cystine, Glycine and Serine Content of Meats. J. C. Alexander, C. W. Beckner, and C. A. Elvehjem. *J. Nutrition* 51: 319, 1953.

The alanine, cystine, glycine, and serine content of 18 samples of beef, lamb, pork, and veal muscle cuts and beef organs were determined by microbiological methods specially modified for this purpose. Where possible, values have been compared with reports in the literature. Cystine, glycine and serine, with average values of 1.1, 5.0 and 5.2 per cent, respectively, were each determined with two micro-organisms, which gave results in good agreement with each other in repeated analyses. Alanine, determined with

one micro-organism, gave an average value of 6.4 per cent. Depending on the amino acid concerned, certain of the beef organs gave higher values than the muscle meats.—B. SURE

Effect of Cooking and of Methionine Supplementation on the Growth-Promoting Property of Cowpea (*Vigna Sinensis*) Protein. F. W. Sherwood, V. Welton, and J. Peterson. *J. Nutrition* 52: 199, 1954.

Dried mature seeds of the cowpea, sometimes called Southern peas, are a staple in the diet of the people in the southern part of the United States. The protein content of these peas varies between 19 to 30 per cent, depending on the variety and the location in which they are grown. The growth-promoting properties of 5 samples of mature cowpea seeds grown in Texas and of 4 samples grown in Oklahoma were measured by incorporating the cowpeas as the source of proteins in the diets of young rats. The 9 samples, representing 8 varieties of cowpeas were fed both raw and cooked, and 6 of the raw cowpea diets were supplemented with methionine.

The differences in the mean growth responses of the rats to the various cowpea diets were not statistically significant. There were, however, indications that the quality of the protein was not the same for all samples of cowpeas and that this variation in quality was associated partially with the variety and partially with the location at which the plants were grown.

Cooking the cowpeas in a double boiler had little effect on the growth-promoting property of some samples but markedly increased the growth response elicited by others. This effect was independent of the location at which the samples were grown. Supplementing the diets containing the raw cowpeas with 0.3 per cent methionine significantly increased the mean gain responses of the animals over those obtained from unsupplemented raw or from the cooked samples.—B. SURE

The popular microbiological assay method for amino acids has been adapted to the determination of the nutritional value of protein. The simplicity of this technique will make it attractive to those who are engaged in the study of the nutritive value of protein foods.

A Rapid Microbial Method of Determining Protein Value. M. J. Horn, A. E. Blum, and M. Womack. *J. Nutrition* 52: 375, 1954.

A rapid method for determining the nutritional value of the proteins of processed cottonseeds has been developed by making a microbiological assay using an enzymatic digest of the meal as the only source of protein in the medium. The method is based on the observation that the sum of the available amino acids determines the amount of growth

of the micro-organism. Since no amino acids are used in the basal medium, the method is relatively inexpensive and results can be obtained in a short time. Unpublished experiments of the authors indicate that the method can be applied to all kinds of foods to detect changes in the nutritive value of protein due to heat, storage, and processing.—B. SURE

It is predicted that the method reported by Murlin for the assay of the biological value of protein based upon the urinary creatinine excretion will find wide application in both human and animal investigation.

Correlation Between the Biological Value of Protein and the Percentage of Creatinine in the Urine. J. R. Murlin, A. D. Hayes, and K. Johnson. *J. Nutrition* 51: 149, 1953.

In a previous publication Murlin and associates pointed out the high correlation found in human subjects between the biological value of proteins and the creatinine excretion in the urine arising from the proteins fed. More convincing evidence is presented in this report of this relationship derived from exactly parallel procedures with 9 dogs. The authors claim that the high degree of correlation between biological values and creatinine nitrogen percentages in the urines of the last days of any given period of protein ingestion entitles this constituent of urinary nitrogen to consideration as a baseline of reference for the evaluation of proteins. With a very poor protein, the amount of nitrogen appearing in the urine is large; the creatinine portion of the total nitrogen, therefore, is a small percentage; and vice versa for a good protein. The correlations arrived at in these experiments lend themselves to prediction of biological values from creatinine nitrogen percentages.—B. SURE

ALCOHOL

Alcohol has been advocated as a source of calories for parenteral use in postoperative patients. Clinical studies have been conducted which suggest that this method of nutritional supplementation is beneficial. However, the actual metabolism of alcohol and its influence upon cellular metabolism with respect to protein, carbohydrate, and fat, has not been thoroughly investigated. Two of the more pertinent recent observations are described below.

Influence of Alcohol Consumption on Hepatic Function in Healthy Gainfully Employed Men. L. Zieve and E. Hill. *J. Lab. & Clin. Med.* 42: 705, 1953.

This is a carefully designed, controlled, and meticulously analyzed study of alleged yardsticks of hepatic function in a group of 744 healthy men. The attempt objectively to characterize and differentiate degrees of alcohol consumption appears to be much

sounder than has been the case with some other assessments of alcohol ingestion. Furthermore, the quantification of liver function measurements (1 minute and total bilirubin, thymol turbidity, zinc sulfate turbidity, cephalin-cholesterol flocculation, colloidal red flocculation, cholesterol esters, brom-sulfalein retention, hippuric acid clearance, galactose tolerance, urine urobilinogen, urine coproporphyrin) is probably inordinately reliable because of accomplishment in a laboratory in the forefront of methodologic investigation of these variables.

In general there was no demonstrable impairment of hepatic function in relation to increasing degrees of alcohol consumption as assessed in terms of the reported histories of the subjects. Unfortunately, the group of allegedly heavy drinkers numbered only 14, so that the possibility of dissimilar findings in a larger group of heavy drinkers remains. Furthermore, the problem of equating the results of subjective rating scales to actual alcohol consumption is a nettling one, since it is difficult to exclude the possibility that individuals rate themselves inaccurately in a nonrandom fashion. Therefore, it is conceivable that (in relation to social stigma) individuals who drink heavily identify themselves with mild and non-drinkers, whereas the latter two groups provide more accurate information.

"Supernormal" results (in heavy drinkers) of serum bilirubin and hippuric acid metabolism are attributed by the authors to increased function of hepatic cells as a consequence of slight damage to them.—R. TARAIL

The Metabolism of Ethyl Alcohol. E. K. Marshall, Jr., and Wm. F. Fritz. *J. Pharmacol. & Exper. Therap.* 109: 431, 1953.

The metabolism of ethanol has been followed by determining its disappearance from the blood. The analytical methods used have been the alcohol dehydrogenase-DPN procedure of Bücher and Redetzki (*Klin Wchnschr.* 29: 615, 1951) and the dichromate oxidation procedure of Harger (*J. Lab. & Clin. Med.* 20: 746, 1934-35). At very low plasma concentrations, the rate of disappearance of ethanol from the plasma is proportional to the amount of alcohol present, as demonstrated by the fact that the disappearance follows an exponential curve. On the other hand, at relatively high concentrations, the rate of oxidation of ethyl alcohol is independent of the amount present, as demonstrated by a rectilinear disappearance curve. The oxidative rate in dogs is not constant, varying from hour to hour and from day to day—in the same dog. The results obtained thus far make it impossible to determine if the rate of oxidation of alcohol is higher at high doses than at lower doses.—C. ALPER

In the experimental animal, alcohol did not alter the hepatic blood flow or the systemic hemodynamics.

Estimated Hepatic Blood Flow in the Dog: Effect of Ethyl Alcohol on It, Renal Blood Flow, Cardiac Output and Arterial Pressure. C. McC. Symthe, H. O. Heinemann, and S. E. Bradley. *Am. J. Physiol.* 172: 737, 1953.

In anesthetized dogs, hepatic blood flow as determined by the bromsulphonphthalein (BSP) technique, was 29.5 ml./Kg./min. (540 ml./min). The following parameters were measured after a narcotizing dose of grain alcohol administered by stomach tube: cardiac output, oxygen consumption, renal blood flow, hepatic blood flow, hepatic BSP extraction, mean arterial blood pressure, total hepatic and renal vascular resistance. None of these showed any statistically significant change after alcohol.—M. J. OPPENHEIMER

NUTRITIONAL ASPECTS OF ANTIBIOTICS

Since the ascendancy of the antibiotic agents, many reports have appeared indicating the value of these substances as feed supplements to farm animals, particularly chicks and swine. It has been widely suggested that growth stimulation in animals is the result of the suppression of intestinal micro-organisms which compete with the animal for the available food supply, or which impair hepatic function through the influence of the absorbed toxic products of their metabolism, or by interference with the absorption of nutrients. One effect observed in animal husbandry has been the stimulation of the appetite by certain of the antibiotics. However, this probably plays a minor role in the growth-stimulating effects observed. Disease-free animals do not respond to antibiotic feeding.

A Mechanism of the Vitamin-Sparing Effect of Antibiotics. W. J. Monson, A. E. Harper, M. E. Winje, C. A. Elvehjem, R. A. Rhodes, and W. B. Searles. *J. Nutrition* 52: 627, 1954.

Numerous reports in the literature have indicated that when animals are grown on diets containing suboptimum amounts of certain vitamins, improved growth can be obtained by supplementing the diets with antibiotics. It was the purpose of this study to provide more information on the mechanism of action of the vitamin-sparing effect of antibiotics.

The growth of chicks fed synthetic diets containing limiting amounts of folic acid was increased by supplementing the diets with antibiotics. The increase in growth was accompanied by the appearance of one or more coliform organisms in the ileum and duodenum contents that produced increased amounts of extracellular folic acid. This change was apparent in two days in the ileum contents of 4-week-old chicks. It was also observed that the increased folic acid production was correlated with increased liver folic

acid, but there was no change in the concentration of intestinal folic acid. These results may explain at least in part the mechanism by which antibiotics spare vitamins for the chick.—B. SURE

Further Evidence as to the Possible Mechanism Involved in the Growth-Promoting Responses Obtained from Antibiotics. R. J. Jacobs, J. F. Elam, G. W. Anderson, L. L. Gee, J. Fowler, and J. R. Couch. *J. Nutrition* 51: 507, 1953.

Data from two separate experiments showed that the oral administration of penicillin, erythromycin, aureomycin, bacitracin, chloromycetin, furazolidone, or *p*-chlorophenylarsonic acid failed to stimulate the growth of chicks reared in clean quarters. These supplements likewise failed to decrease the total number of *clostridia* present per gram of feces. This is further evidence that antibiotics stimulate growth by reducing the total number of *clostridia* in the intestinal tract of the chick and are ineffective in stimulating growth in a clean environment where the *clostridia* population is low.—B. SURE

Antibiotics, Methionine and Unidentified Growth Factors in the Nutrition of Broadbreasted Bronze Turkey Poults. R. A. Atkinson, B. L. Reid, J. H. Quisenberry, and J. R. Couch. *J. Nutrition* 51: 53, 1954.

Previous investigators have reported unidentified growth factors for the turkey poult to be present in dried skim milk, fish meal, dried whey, fish solubles, distillers' dried solubles, dried brewers' yeast, liver preparations, grass and alfalfa juices.

From the results of this study it became apparent that bacitracin and penicillin will increase growth and improve feed efficiency when added to an all-vegetable protein diet for turkey poults. DL-methionine produced an increase in growth and improvement in feed efficiency when 0.05 per cent was added to the basal diet. The response was shown to be additive with that due to the unidentified factor content of distillers' dried solubles, and was further increased by the addition of an antibiotic to such a ration.

Distillers' dried solubles contain an unidentified poult growth factor. The content of such factor in this product varied in different samples obtained from the same manufacturers. No explanation of such variance is apparent from the data presented.—B. SURE

IRON

Several methods have recently been presented for the evaluation of iron stores in the body. One of these deals with the evaluation of hemosiderin granules observed directly in unstained bone marrow preparations. In the presence of iron-deficiency anemia there is a lack of hemosiderin granules. This

is a reflection of the reduction in tissue iron stores which occurs when an iron-deficiency anemia exists.

Iron Metabolism: Clinical Evaluation of Iron Stores. A. R. Stevens, Jr., D. H. Coleman, and C. A. Finch. *Ann. Int. Med.* 38: 199, 1953.

It would appear from previous work that hemoglobin has priority for body iron and that when iron-deficiency anemia exists, a depletion of iron stores exists. This assumption is enhanced by these studies, in which the amount of iron present in the bone marrow in the form of hemosiderin is estimated in a variety of hematologic disorders. The authors found that the lack of hemosiderin granules, which were observed directly in unstained marrow particles, correlated quite well with a state of hypochromia. It appeared to be particularly useful in differentiating true iron-deficiency anemia from the anemia of infection. It should be noted, however, that the mean corpuscular hemoglobin concentration (MCHC) did as well in this differentiation. Of interest is the demonstration (again) that women in the child-bearing age have a very tenuous iron reserve which makes them more liable to iron deficiency than men. It would seem that this technique of estimating the iron stores is a valuable aid in deciding upon the use of iron therapy.—J. F. MUELLER

Iron-deficiency anemia secondary to hemorrhage is associated with reduced levels of serum iron; these levels are also reduced in individuals who have gastric cancer. It has been observed that after administration of oral iron the serum iron levels will increase when the anemia is due to blood loss, whereas in the case of carcinoma there is no significant increase in the serum iron. This determination may prove to be a useful clinical appurtenance.

The Significance of Serum Iron in the Differential Diagnosis between Gastric Carcinoma and Peptic Ulcer. K. A. Fredrikson. *Acta med. scandinav.* 146: 259, 1953.

A study in patients with gastric and duodenal ulcer, gastric carcinoma, and other malignant diseases revealed that the serum iron is likely to be normal in patients with peptic ulcer except where hemorrhages have occurred. Following blood loss, the serum iron is low. On the other hand, in cancer the serum iron level is generally low, even when there is no marked anemia or obvious hemorrhage. The serum iron level, therefore, may be of some value in the early diagnosis of gastric carcinoma.

The rise in serum iron after administration of oral iron was studied and it was found that whereas in peptic ulcer there is a rise in serum iron, in cancer the serum iron rises very little after the iron test, independently of whether or not anemia or hemorrhages are present.—S. O. WAIFE

Radioactive iron has proved an extremely useful tool in the study of the absorption, transport, and utilization of this mineral in human and animal nutrition. The following study indicates that the parenteral administration of iron results in the formation of hemosiderin, which is then gradually converted to ferritin.

Uptake and Storage of Radioactive Iron by Mouse Liver. J. K. Hampton, Jr., and J. B. Kahn, Jr. *Am. J. Physiol.* 174: 226, 1953.

After intravenous injection of 75 micrograms of radioactive iron, the liver had taken up most of it in the hemosiderin fraction in 3 hours. After 15 hours the hemosiderin had decreased and ferritin had increased an equal amount. There was not any change in the next 33 hours. Equilibrium in the tissues showed a ferritin-hemosiderin ratio of just above 1. Doses of iron from 12.5 to 125.0 micrograms did not change these ratios when examined 15 hours after injection. The authors are of the opinion that iron is taken up rapidly in a form like hemosiderin and then later changed to ferritin. Equilibrium is established before 15 hours.—M. J. OPPENHEIMER

Intravenous iron has been recommended only for those patients unable to tolerate oral iron therapy. The advantage claimed for intravenous therapy is that it rapidly provides iron for hemoglobin formation and will quickly saturate the depleted iron stores. However, severe toxic reactions and fatalities have been reported.

Toxic Reactions Due to Intravenous Iron. I. M. Librach. *Brit. M. J.* 1: 21, 1953.

Two cases of toxic reactions to intravenous iron are reported. Both patients were young females suffering from tuberculosis and anemia. In one case, the most dramatic toxic manifestation was an epileptiform fit one minute after injection of 100 mg. of "Ferrivenin." The second patient had a long history of "asthma." Severe dyspnea and cyanosis (relieved by intravenous epinephrine) occurred within two minutes of injection of 100 mg. of "neo-ferrum." Subsequently this patient tolerated doses of 60 mg. or less.

The theories regarding the origin of toxic responses to intravenous iron are reviewed, and the author places a good deal of stress on a possible allergic mechanism. It is pointed out that the most severe reactions recorded in the literature occur after doses of 100 mg. or more—H. L. TAYLOR

Clinicians interested in the physiology and morphology of iron in the human body will find the following review paper useful.

Iron Deposits in the Body and their Pathologic Significance. A Review. G. S. Strassman. *Am. J. Clin. Path.* 24: 453, 1954.

Dr. Strassman has been interested in iron deposits in man, especially in the central nervous system, for many years. This is a straightforward review of 237 papers concerned with the pathologic significance of such deposits prepared particularly for pathologists. A short history of morphologic discoveries is followed by a discussion of histochemical technique. Despite the limitations of the method, its utilitarian value is emphasized. The fundamentals of iron metabolism are summarized briefly. The discussion of iron deposits in the brain is commensurate with the author's special interest in this aspect of the problem. Localized hemosiderosis is discussed briefly.

Lastly, three and a half pages are devoted to endogenous hemosiderosis, hemochromatosis, exogenous hemosiderosis, and transfusion siderosis.—J. GRUHN

THE ROLES OF VITAMIN B₁₂

Recent studies indicate that vitamin B₁₂ administration results in an increased fat content of animal carcasses. Animals maintained on a vitamin B₁₂-deficient diet have a lower fat content than normal animals. In addition, it has been observed that the sulfhydryl content of blood is abnormally reduced in patients with pernicious anemia and in experimentally vitamin B₁₂-deficient animals. These findings indicate that vitamin B₁₂ may be involved in fat and carbohydrate metabolism. Further studies along these lines are presented in the following papers.

The Influence of Vitamin B₁₂ on Carbohydrate and Lipide Metabolism. C. T. Ling and B. F. Chow. *J. Biol. Chem.* 206: 797, 1954.

This paper describes further studies on the possible relationship between the metabolic changes in carbohydrate and lipid metabolism of glutathione concentrations in the blood and tissues. The glucose tolerance curves of vitamin B₁₂-deficient rats was markedly elevated 60 minutes after glucose injection, as compared to curves obtained from vitamin B₁₂-injected rats. The injection of vitamin B₁₂ in littermates resulted in a threefold increase of total phospholipids in the lean tissues of the carcass as well as a higher phospholipid content per unit weight of tissues. Two cases of pernicious anemia, observed to determine the effect of the ingestion of 3 mg. of vitamin B₁₂ on total phospholipid, indicated that in one patient, a 56-year-old male, the phospholipid increased from 57 to 253 mg. per 100 ml. of blood, and in another case, a 63-year-old male, the administration of 3 mg. of vitamin B₁₂ orally increased the phospholipid from 185 to 245 mg. per cent, respectively.

Since glutathione levels are markedly diminished in vitamin B₁₂-deficient animals, an attempt was made

to determine the effect of added glutathione on the blood sugar levels of rats. It was shown that glutathione, like vitamin B₁₂, lowered the blood sugar levels of rats with hyperglycemia induced by a high carbohydrate-low fat diet and by glucose injections.

The rapidity with which the vitamin B₁₂-deficient rats lost body weight and developed hyperglycemia under the influence of a high carbohydrate-low fat diet, and the reported increased requirements of vitamin B₁₂-deficient rats for this vitamin when raised on such a diet, suggest to the authors that the deficient animals have lost part of their ability to transform carbohydrate into lipids. The relatively small amounts of phospholipid found in the tissues of B₁₂-deficient rats were thought to confirm this hypothesis.—M. K. HORWITT

Effect of Vitamin B₁₂ on Liver and Blood Non-Protein Sulphydryl Compounds. U. D. Register. *J. Biol. Chem.* 206: 705, 1954.

This paper reports on an investigation into the effects of vitamin B₁₂ on the levels of ergothioneine, glutathione, and total nonprotein sulphydryl groups in the liver and blood of rats. Weanling rats born to mothers maintained on vitamin B₁₂-deficient diets were continued on the deficient diets, and their weight gains, liver and blood values for ergothioneine, glutathione, and total nonprotein sulphydryl groups were determined and compared with those obtained from animals which had received the same diet plus injections of vitamin B₁₂. There was a marked decrease in the levels of liver and blood sulphydryl groups in the B₁₂-deficient animals. The difference was largely due to glutathione. There was no significant effect on the liver or blood ergothioneine.—M. K. HORWITT

This vitamin is also involved in the synthesis of purines and in the production of nucleoproteins, possibly by potentiating the formation of citrovorum factor from folic acid.

Metabolic Interrelationship Between Folic Acid, Vitamin B-12 and the Citrovorum Factor. V. M. Doctor, B. E. Welch, R. W. Perrett, C. L. Brown, S. Gabay, and J. R. Couch. *Proc. Soc. Exper. Biol. & Med.* 84: 29, 1953.

The authors wished to determine the effect of supplementation of chick diet with varying levels of vitamin B₁₂ and of pteroylglutamic (folic) acid on the *in vitro* synthesis of citrovorum factor (folinic acid) from added pteroylglutamic acid by liver homogenates. They found that supplementing a low vitamin B₁₂, low pteroylglutamic acid chick diet with either increasing levels of vitamin B₁₂ or increasing levels of pteroylglutamic acid resulted in an increased capacity by the liver homogenates to convert added pteroylglutamic acid to citrovorum factor. *In vitro*

addition of "formate" plus vitamin B₁₂ to liver homogenate gave only a slight stimulation to the conversion of pteroylglutamic acid to citrovorum factor by the homogenate.—L. W. KINSELL

Vitamin B₁₂ and Folic Acid in Milk Diets. R. A. Collins, M. Schreiber, C. A. Elvehjem, and E. B. Hart. *J. Nutrition* 49: 485, 1953.

In spite of the discovery that iron and copper could cure cow's milk anemia, a number of European workers reported the failure of these minerals to cure anemia produced in rats and infants as a result of goat's milk feeding. Since liver, liver extracts, and yeast were found to cure this condition, it was suggested that goat's milk may be deficient in vitamin B₁₂, which proved to be the case. The inferior growth of rats fed a mineralized goat's milk diet was found to be the result of a vitamin B₁₂ deficiency. Rat growth equal to that obtained with a cow's milk diet was obtained when 0.5 µg. of vitamin B₁₂ was added per rat per day to a goat's milk diet, or when 3 µg. of vitamin B₁₂ was added per liter of goat's milk.

Folic acid spared a part of the vitamin B₁₂ requirement of the rat fed a mineralized goat's milk diet. Folic acid and vitamin B₁₂ additions to mineralized goat's milk or cow's milk diets did not influence the rate of hemoglobin formation in the normal or the anemic rat.—B. SURE

Stress and cortisone with their ubiquitous effects apparently also modify vitamin B₁₂ metabolism.

Decreased Resistance of Vitamin B₁₂-Deficient Rats to Cold Stress. B. H. Ershoff. *Proc. Soc. Exper. Biol. & Med.* 84: 615, 1953.

Rats, maintained at a temperature of $2 \pm 1.5^\circ \text{C}$., had a significantly higher vitamin B₁₂ requirement than did animals maintained under normal laboratory conditions. Survival of B₁₂-deficient rats under cold room conditions was significantly diminished as compared to normal animals.—L. W. KINSELL

Prevention by Vitamin B₁₂ of Protein Catabolic Action of Cortisone. J. Meites and Y. S. L. Feng. *Proc. Soc. Exper. Biol. & Med.* 85: 341, 1954.

Vitamin B₁₂ exerts a protective action against the net protein catabolic effects of cortisone in animals fed an *ad lib* diet, but it is ineffective when the food intake is reduced to that of rats given cortisone without vitamin B₁₂. In view of the observations of Engle, who noted that administration of glucose or amino acids to fasting nephrectomized rats prevented the usual increase in blood urea elicited by injecting adrenal cortical extracts, the authors conclude that vitamin B₁₂ exerts a nitrogen-sparing effect by increasing appetite and food intake, and thus increasing the availability of glucose and/or amino acids to the organism.—L. W. KINSELL

Studies comparing aging patients and those of younger ages disclose a decrease in vitamin B₁₂ excretion with advancing age. Whether this decrease in urinary excretion in the older group is due to changes in renal function with age, a difference in the bound vitamin B₁₂ in the blood serum, or other factors is not clear.

Agewise Differences in the Urinary Excretion of Vitamin B₁₂ Following Intramuscular Administration. D. M. Watkin, C. A. Lang, B. F. Chow, and N. W. Shock. *J. Nutrition* 50: 341, 1953.

In this communication the results of measurements of the urinary excretion of vitamin B₁₂ by healthy individuals of divergent ages are presented. The urinary excretion of vitamin B₁₂ following its intramuscular administration in crystalline form was studied at 20, 30, 50, and 75 μ g. dose levels in groups of male subjects, aggregating 107 individuals in widely separated age categories. In the first study, a young group averaging 29.7 years excreted significantly more vitamin B₁₂ than did an old group averaging 76.4 years. In the second study, an orderly and significant decrement in vitamin B₁₂ excretion was observed from young (28.0 years) to middle (61.4 years), to old (81.6 years), groups. The decrement in vitamin B₁₂ excretion with age parallels decrements in renal function with age. However, so small a fraction of administered vitamin B₁₂ appears in the urine that the observed differences cannot be attributed to renal factors alone.—B. SURE

One of the most interesting aspects of this remarkable vitamin is the fact that it appears both as bound and free vitamin B₁₂ in the serum. Since our understanding of the inner workings of metabolism must concern this "binding," the following paper is of considerable interest.

Observations on the Bound Form of Vitamin B₁₂ in Human Serum. W. R. Pitney, M. F. Beard, and E. J. van Loon. *J. Biol. Chem.* 207: 143, 1954.

The vitamin B₁₂ which is normally present in the circulation exists primarily in combined form as a labile complex with serum protein. Free vitamin B₁₂ can be split off from this complex when the proteins are denatured by heat. The green alga, *Euglena gracilis*, is sensitive only to the free form of the vitamin so that its growth can be used as a means of determining free vitamin B₁₂. Thus, the difference between the heated and the unheated preparation enables the concentration of vitamin B₁₂ in the bound form in serum to be calculated.

The total vitamin B₁₂ concentration of thirteen normal sera was found to vary from 122 to 460 μ g/m.

per ml. with a mean value of 195 μ g/m. per ml. In ten of the thirteen sera, all of the vitamin B₁₂ was estimated to be in the bound form. In the other three, small amounts of the free vitamin were present. The binding of vitamin B₁₂ by normal serum was studied in two ways: (a) the total binding capacity following the addition of excess crystalline vitamin B₁₂ was determined, and (b) the location of the bound vitamin in serum was investigated by an electrophoretic technique. Upon the addition of 1000 μ g/m. of crystalline vitamin B₁₂ to 1 ml. of serum, the mean concentration of bound vitamin increased from 178 to 336 μ g/m. per ml.

α -globulin fractions were specifically responsible for the binding of the B₁₂ in the serum. Serum albumin was not considered to play a part in the transport of vitamin B₁₂ in the circulation, and the other globulin fractions likewise had little activity in this respect. The authors point to the theoretical possibility that a megaloblastic anemia could be caused by a deficiency in vitamin B₁₂-binding material. Attention is called to a case reported by Horrigan and Heinle (*J. Lab. & Clin. Med.* 40: 811, 1952) in which a tracer dose of radioactive vitamin B₁₂ was largely lost in the urine, indicating inability of the body to bind the vitamin. A hematological remission was induced by intravenous infusion of 250 ml. of normal plasma.—M. K. HORWITT

Radioactive cobalt-labeled vitamin B₁₂ has been employed in studies concerning the absorption and utilization of this vitamin. By this means it has been shown that patients with pernicious anemia in remission will have a high fecal loss of the cobalt label. The radioactive vitamin was fed with normal gastric juice with results as noted below.

Oral Administration of Co⁵⁷ Vitamin B₁₂ to Normal Persons, Patients with Pernicious Anemia, and Subjects with Various Medical Disorders. L. M. Meyer, A. Becerra-Garcia, A. Goldman, and P. A. Stern. *J. Appl. Physiol.* 6: 263, 1953.

Following the oral administration of radioactive (Co⁵⁷) cobalt-labeled vitamin B₁₂, normal persons excreted from 8 to 41 per cent of the cobalt in their stools. A wider range, from 11 to 100 per cent of administered activity, was excreted by patients with cardiac disease, hepatic cirrhosis, rheumatoid arthritis, and lymphomatous diseases. There seemed to be no relationship between the excretion of Co⁵⁷ and free hydrochloric acid in the gastric juice. Patients with pernicious anemia had an excretion ranging from 48 to 100 per cent. When 100 ml. of neutralized normal gastric juice was added, there was a reduced fecal radioactivity in some patients. It is significant that folic acid and hog duodenal mucosa extract did not alter the excretion of radioactive cobalt in patients with pernicious anemia.—S. O. WAIFE

LIPIDS

Accumulations of hepatic fat following the administration of choline-deficient diets have been studied repeatedly. The ability of choline or other methyl donor substances to prevent fatty metamorphosis of the liver is well established. It has now been shown that in animals, choline-deficient, high fat diets will result in the production of intimal and medial deposits of lipid in the cardiovascular system. Again, choline supplementation was able to prevent these lipid deposits.

Abnormal Lipid in Coronary Arteries and Aortic Sclerosis in Young Rats Fed a Choline-Deficient Diet. G. F. Wilgram, W. S. Hartroft, and C. H. Best. *Science* 119: 842, 1954.

Young rats on a high fat, low choline diet rapidly develop lipid deposits in the walls of the coronary arteries and the aortas. In this study, young rats were divided into two groups. The majority ingested a diet unsupplemented in choline, while the control group was fed a similar basal diet supplemented with 0.85 per cent choline chloride. At the end of a full week period, histological examinations revealed significant differences in the two groups.

Abnormalities of the cardiovascular system were absent in all the choline-supplemented controls but developed in 22 per cent of the choline-deficient rats. The aortic lesions consisted of intimal and medial deposits of lipid, frequently associated with pathological amounts of calcium salts in the media.

Grossly evident aortic sclerosis was rarely found in the absence of renal damage. From these and other studies, the authors conclude that the evidence indicates that an adequate intake of choline favors the maintenance not only of a healthy liver and kidney but also of a normal cardiovascular system in young rats; and, as they also state, it will obviously be necessary to confirm these findings in other species of laboratory animals before their possible clinical significance is considered. The term "lipotropic" perhaps may now be extended to include the prevention of the accumulation of stainable fat, not only in the liver and kidneys but also in the heart and blood vessels of animals exhibiting such lesions when choline and its precursors are absent in the diet.—S. O. WAIFE

Choline and other lipotropic agents were administered with a low fat, low cholesterol diet to patients with arteriosclerosis. No significant alteration in the blood lipid levels were noted over a three-year period.

Clinical Studies in Blood Lipid Metabolism. IX. Effect of Lipotropic Agents on Serum Lipid Partitions in Fifty Patients with Generalized Athero-

sclerosis. A Three Year Study. A. A. Goldbloom, H. B. Eiber, and L. J. Boyd. *Am. J. Dig. Dis.* 21: 152, 1954.

Thirty male and 30 female patients with a clinical diagnosis of generalized atherosclerosis and chronic coronary artery disease were maintained on a low fat, low cholesterol diet for 36 months. Fifty of the patients completed the three-year study. Half of the group were also instructed to take 9 to 12 capsules daily of a lipotropic preparation containing choline, methionine, inositol, vitamin B₁₂, liver concentrate, and desiccated liver.

Study of fat partition every six months during the three-year period failed to reveal any significant differences in cholesterol, total lipids, neutral fat, or phospholipid between the control group and those receiving lipotropic agents.

The authors feel that a low fat, low cholesterol diet will attain the same end result as lipotropic agents upon reducing serum lipid partitions.—S. H. LORBER

In untreated diabetes, the fatty acid fraction of serum lipids becomes significantly elevated. It is possible that this is a reflection of the increased mobilization of fat from peripheral depots to the liver. This explanation has also been suggested for the hyperlipemia observed in nephrosis.

Serum Lipids in Normal and Alloxan Diabetic Rats. R. N. Cagan, A. E. Sobel, R. A. Nichols, and L. Loewe. *Metabolism* 3: 168, 1954.

Untreated diabetics, human and animal, show elevated levels of serum cholesterol and total lipids. In the present study, the serum total fatty acids, total cholesterol, and phospholipids were found to be elevated in diabetic rats. It is the fatty acid fraction which shows the most significant elevation, while increases in cholesterol and phospholipid are smaller and less uniform.—C. R. SHUMAN

Fat Metabolism in Nephrotic Hyperlipemia. W. Heymann, L. W. Matthews, J. Lemm, P. Olynnyr, M. Salchar, and C. Gilkey. *Metabolism* 3: 27, 1954.

Emulsions of C¹⁴-labeled trilaurein were given intravenously to 16 rats with nephrotoxic renal disease and 15 control rats. Utilization of trilaurein was determined by counting the expired C¹⁴ in a respirometer. The specific activity was low in 5 and normal in 11 nephrotic rats. The degree of hyperlipemia was independent of the rate of trilaurein utilization in these animals. The clearance of this substance from the blood stream proceeded at equal rates in both groups. The results of the present study favor the concept that nephrotic hyperlipemia is due to an increased mobilization rather than to a faulty deposition or utilization of lipids.—C. R. SHUMAN

Administration of thyroid extract has been found to lower the level of serum lipids. With respect to cholesterol, it has been shown that thyroid extract increases the rate of destruction of this molecule.

Effect of Thyroid Extract on Serum Lipoprotein and Serum Cholesterol. B. Strisower, J. W. Gofman, E. F. Galioni, A. A. Almada, and A. Simon. *Metabolism* 3: 218, 1954.

The administration of 10 grains of thyroid extract daily to 19 euthyroid schizophrenic patients produced a significant lowering of serum cholesterol, S_r 0-12 and S_r 12-20 lipoproteins. In 4 normal subjects a similar reduction was observed in these lipids. Responses were of borderline significance in the S_r 20-400 band of lipoproteins. Of possible significance is the fact that a state of negative caloric balance accompanied the cholesterol and lipoprotein lowering. The magnitude of the drop in cholesterol and S_r 0-20 lipoproteins was positively correlated with the initial levels of both measures.—C. R. SHUMAN

Lipoproteins in Infectious and Serum Hepatitis. F. T. Pierce, Jr., J. R. Kimmel, and T. W. Burns. *Metabolism* 3: 228, 1954.

Blood samples were obtained from 33 patients with infectious hepatitis and 15 patients with serum hepatitis for determination of the lipoprotein spectrum by ultracentrifugation at the Donner Laboratory. It was found that the classes of lipoprotein below S_r 0-12 peak were increased in all patients. These measurements did not aid in differentiating infectious from serum hepatitis. A positive correlation was obtained between the lower S_r lipoprotein classes and the degree of elevation of the icterus index and serum bilirubin. With an icterus index below 10 there was no significant correlation with the lipoproteins. However, there was a significant rise in S_r 12-20 and fall in S_r 100-400 in those patients with an icterus index above 10.5. No significant correlation was observed between the lipoproteins and the albumin/globulin ratio, or flocculation tests except for thymol turbidity which correlated with the entire S_r 0-400 group of lipoproteins. The return of lipoprotein levels to normal during convalescence parallels the return of the icterus index to normal.—C. R. SHUMAN

The interconversion of lipoproteins from one S_r class into a different S_r class has been reported in various diseases and following the administration of a variety of agents. The site of these conversions and their significance are not entirely clear at this time. The possibility that the liver is involved either in the production of the various S_r classes or their interconversions is suggested in the following paper dealing with lipoproteins in patients with hepatitis.

The Interconversion of Serum Lipoprotein in vivo. F. T. Pierce, Jr. *Metabolism* 3: 142, 1954.

In cholesterol-fed rabbits, there exist in the serum large quantities of all classes of lipoprotein as determined by ultracentrifugation. In the normal rabbit only trivial amounts of lipoprotein are found in the S_r 5-15 class. The authors injected serum from cholesterol-fed rabbits into normal rabbits in order to study the fate of isolated classes of lipoprotein in the recipient rabbits' serum. Within a few hours the high S_r rate lipoproteins were converted into lower S_r rates in a serial fashion. The conversion never occurred in the reverse direction. The injected S_r 5-15 lipoproteins disappeared from the serum; this disappearance occurred at a slower rate than conversion of the higher S_r lipoproteins to this class.—C. R. SHUMAN

Further evidence is presented supporting the concept of direct absorption of fat into the bloodstream from the gastrointestinal tract.

Particulate Fat Absorption and Secretion. H. Singer, J. Sporn, and H. Necheles. *Gastroenterology* 26: 299, 1954.

Three dogs weighing between 9 and 10 Kg. were prepared with thirty fistulas, consisting of a 40 cm. segment of jejunum just distal to the ligament of Treitz.

Cocoonut and olive oil were introduced into these segments and chylomicron counts were done hourly for five hours. Checks were also made for the presence of bile, lipase, and pH. The pH was never over 7, and usually ranged between 6.1 and 6.3. Lipase was found to be present in all specimens. In no sample was bile found.

In two of the three dogs, chylomicronemia was consistently produced. The third varied in response, but on two occasions did show absorption. The smallest amount of fat necessary to produce chylomicronemia was 5 ml. Peak absorption usually occurred between the second and third hour.

Fasting loop secretions were found teeming with brilliant, dancing particles, which the authors believe are similar in appearance to chylomicrons. They have named these particles enterolipomicros. The authors suggest that bile salts and pancreatic lipase are not necessary for particulate fat absorption.—S. H. LORBER

ITEMS OF GENERAL INTEREST

The Impact of Vitamin Research upon Medical Practice. V. P. Sydenstricker. *Proc. Brit. Nutrition Soc.* 12: 256, 1953.

Some sort of knowledge of the specific curative effects of liver, fresh milk, muscle meat, and some fruits and vegetables for certain diseases has been available since early times. The Egyptians knew that

fish livers were good for night blindness, and the Chinese knew more than 3000 years ago that the liver of almost any animal helped some forms of anemia. American Indians four hundred years ago knew that infusion of spruce or pine needles cured scurvy.

In the application of vitamin research to the practice of medicine, it is important to stress the multiple nature of deficiency states. A diet sufficiently inadequate to produce clinical symptoms is usually, if not always, lacking in several vitamins and in protein, fat, iron, and calcium as well. The fact that the presenting symptoms and signs of beriberi can be cured with thiamine or those of scurvy with ascorbic acid does not invalidate this statement. When therapy with nicotinic acid exposed the riboflavin deficiency in pellagra the concept of multiple deficiency states became apparent.

The importance of iron and protein must be emphasized. Anemia is common to almost all nutritional diseases.

There are rather definite indications for the use of vitamins. In the presence of endemic diseases, such as pellagra, beriberi, or rickets, the specific vitamins in therapeutic amounts and in appropriate mixtures should be employed until such a time as adequate intake and assimilation of proper food can be assured. Also, vitamins must be added to inadequate diets prescribed for the management of certain diseases, notably those used in hypertension, peptic ulcer, and obesity. Occasionally patients who have had resection of massive segments of the gastrointestinal tract will need large vitamin supplements to compensate for faulty absorption. In patients chronically ill who must be subjected to surgery, preparation for operation involves the use of vitamins.

Healthy people eating a normal diet do not need added vitamins. Vitamins will not cure the ailments of the psychoneurotic or the inertia and insomnia of the depressed. Neither are the vitamins "a pick-me-up" for the tired and hungry. Vitamin pills in no way can replace food, and as placebos vitamins are extraordinarily expensive.—B. SURE

The Effects of Nutritional Deficiency on Response to Thiopental. H. A. Levy, J. R. DiPalma, and C. Alper. *J. Pharmacol. & Exper. Therap.* 109: 377, 1953.

This report emphasizes the role of the nutritional status of the experimental animal in response to thiopental.

The response of mice made deficient in protein, B-complex vitamins, and individually deficient in thiamine, niacin, riboflavin, pyridoxine and pantothenate, has been investigated by means of a new technique. This method measured the ability of the trained mouse to escape from an unpleasant stimulus, a hot plate at 65° C., by climbing and holding onto a roughened, sharply inclined surface within a given

time limit. With this technique, it was possible to measure the intensity of response to thiopental, with actual responses including: intact responses, lack of muscular co-ordination, hypnosis, anesthesia, and death. When normal animals were tested, about 50 per cent successfully climbed the inclined plane, whereas the remainder failed to climb, but none were anesthetized. This dosage, which in these particular experiments turned out to be 37 mg./Kg., has been named the Plane Dose-50 (PD₅₀).

Mice made deficient in thiamine demonstrated essentially a normal response. B-complex, riboflavin, pyridoxine, and pantothenate-deficient animals showed a moderately enhanced response to the PD₅₀ of thiopental. Protein-deficient mice also demonstrated a moderately enhanced response to the PD₅₀ of thiopental. Mice made deficient in niacin by a diet of poor quality protein, low in tryptophane and with an amino acid imbalance, demonstrated a significantly enhanced response to the PD₅₀ dose of thiopental. Almost half of the niacin-deficient animals were anesthetized by the dosage of thiopental. The possible role of the pyridine nucleotide-linked enzymes in the metabolic transformation of thiopental is discussed.—C. ALPER

The Effect of Feeding Large Amounts of Emulsifiers Polyoxyethylene (20) Sorbitan Monostearate (Tween 60) and Sorbitan Monostearate (Span 60) to Humans. S. S. Waldstein, H. M. Schoolman, and H. Popper. *Am. J. Dig. Dis.* 21: 181, 1954.

To evaluate the pharmacologic effect of emulsifying agents commonly used in commercial foods, a group of 44 patients of an old people's and chronic disease infirmary were fed daily for 28 days large amounts of emulsifying agents in six-gram doses. Nineteen patients were given Tween 60®, 16 were given Span 60®, and 9 were given corn oil placebos.

No specific complaint was registered by the patients, and physical findings remained unchanged in all subjects.

Studies included urinalysis, hemagram, a battery of liver function tests, nonprotein nitrogen, blood urea nitrogen, and creatine. No significant changes occurred in these tests during the period of observation.—S. H. LORBER

Cortisone in Portal Cirrhosis: A Controlled Study. S. J. Zockler. *Gastroenterology* 26: 878, 1954.

The authors attempted to assess the therapeutic efficacy of cortisone in portal cirrhosis. Thirty-six male patients with cirrhosis were divided into four groups for the study:

Group I—Nine patients with portal cirrhosis and ascites, treated with diet and cortisone. Group II—Nine patients with portal cirrhosis and ascites treated with diet alone. Group III—Eight patients with portal cirrhosis and no evidence of decompensation,

treated with diet and cortisone. Group IV—Ten patients with portal cirrhosis and no evidence of decompensation, treated with diet alone.

All patients received a 4300 calorie diet. In addition, they received concentrated vitamins and yeast tablets. Cortisone was administered as follows: 300 mg. the first day, 200 mg. the second, and then 100 mg. daily until 14 days had elapsed.

The most significant change observed was a rise in the serum albumin concentration in Group I. Three patients had normal values before therapy and 7 after therapy.

Serum bilirubin declined in both the control and treated groups during the period of study. Bromsulphalein retention, elevated in all groups before therapy, showed significant improvement during the period of observation. Similar improvement was noted in other liver function tests.

Microscopic examination of hepatic tissue obtained by biopsy failed to reveal any essential change during the period of study, or between the control and treated groups. In no case did the severity of fatty metamorphosis increase during the observation period. Thus the authors conclude that the only specific effect noted after the addition of cortisone to the dietary program was the beneficial effect on the plasma protein concentration.—S. H. LORBER

Zinc Metabolism of Young College Women on Self-Selected Diets. H. M. Tribble and F. L. Scoular. *J. Nutrition* 52: 209, 1954.

Thirteen college women, 17 to 27 years of age, participated voluntarily in this study while living in a Home Management House. The meals consumed by two groups of the college women were planned cooperatively. Each group, however, purchased and prepared its food separately.

Self-selected diets furnished from 9.8 to 14.4 mg. of zinc daily. The subjects excreted from 0.6 to 1.8 mg. of zinc in the urine and from 3.2 to 7.9 mg. in the feces. An average of 8 per cent of the ingested zinc was excreted in the urine and 42 per cent in the feces. All of the subjects were in positive zinc balance and retained an average of 6.6 mg. per day.—B. SURE

Influence of Diet on Serum Alkaline Phosphatase in Rats and Men. M. Sukumaran and W. L. Bloom. *Proc. Soc. Exper. Biol. & Med.* 84: 631, 1953.

In normal and adrenalectomized rats, the serum alkaline phosphatase is lowered very significantly by fasting. There is no elevation of the phosphatase following feeding of carbohydrates or protein, whereas fat feeding results in a return to or near normal. Fragmentary data in human subjects indicate much the same pattern of response, although to a much lesser degree. The authors cite the work of Tuba and Robinson demonstrating that the alkaline phosphatase

of rat serum is composed of a fraction unaffected by fasting, and a second larger portion which responds relatively quickly to fasting and to ingestion of fat. It is believed that the variable fraction is largely derived from the intestine, where it is essential in the absorption of fat.—L. W. KINSELL

Planning Food Supplies for Tropical Expeditions. B. S. Platt, and R. H. Fox. *Proc. Brit. Nutrition Soc.* 13: 53, 1954.

A tropical climate is an aggressive climate and must be met aggressively. To be able to do this effectively the influence of a hot climate on man must first be understood and then, armed with this knowledge, it is possible to plan ahead to meet the special requirements of life in the tropics. In the present paper the manner in which a tropical climate affects man's dietary needs and habits, and the general principles guiding the planning of food supplies are discussed. The precise requirements of food and equipment for any one expedition must of course depend on the number of individuals, the amount of transport, the availability of local supplies, and the location and duration of the expedition. Ideal requirements may have to be modified to conform to a "cost ceiling."

The dietaries of a typical Himalayan expedition and of the 1953 Everest expedition are described. Himalayan expeditions usually live off the country, supplementing local food from bulk stores. The 1953 party had composite rations, thus providing a more variable and palatable diet than is possible for a party living mainly off the country. The sudden change to a strange and bulky diet at the beginning of the expedition was avoided by using composite rations. Climbers living at altitudes above 19,000 ft. usually consume about 12 oz. sugar a day, and a large proportion of their food takes the form of sugar dissolved in beverages. They develop strange food cravings and prefer to do without rather than eat food that is unpalatable to them. The Everest party in 1953 ate normal food up to 21,000 ft. This was explained by better acclimatization, the greater palatability of the composite ration, and the use of pressure cookers.

The general physical condition of the members of the 1953 expedition was considered to be better than on the 1952 expedition, and the loss of body weight which is characteristic of sojourn at high altitude was less than on previous expeditions.—B. SURE

Distribution of the Xanthine Oxidase Factor (Molybdenum) in Foods. W. W. Westerfield and D. A. Richert. *J. Nutrition* 51: 85, 1953.

Previous studies by these investigators have demonstrated the dependence of intestinal xanthine oxidase on an unidentified dietary constituent which was re-

ferred to as the "xanthine oxidase factor." This factor has been recently identified as the trace element molybdenum (Mo). The present report describes the distribution of the xanthine oxidase factor in a large number of foods, as measured by bioassay procedures. Many foods were also analyzed for Mo chemically, and a comparison of the two values showed that, while the assay results generally paralleled the total Mo content, only a part of the total Mo present in foods was usually available for the biological response.

Foods were assayed for available Mo by determining the intestinal xanthine oxidase response to the incorporation of the food into an otherwise purified Mo-deficient diet. When the results were compared with the total Mo determined chemically, 50 to 100 per cent of the dietary Mo was usually available for the biological response.

Foods considered to be good sources of Mo (arbitrarily containing more than 0.6 p.p.m. of available Mo on a dry weight basis) included: legumes, cereal grains, some dark green leafy vegetables, and liver, kidney, and spleen among the animal tissues. Fruits, berries, and most root or stem vegetables were relatively poor sources of Mo, inasmuch as they contained less than 0.1 p.p.m. Brewers' yeasts were good sources of Mo and bakers' yeasts were poor sources, even though the growth media in both cases were not rich in Mo.—B. SURE

On the Mechanism of Action of α -Tocopheryl Phosphate with Special Reference to Carbohydrate Metabolism of Striated Muscle. I. Modification of Epinephrine Effect (Hyperlactacidemia) by α -Tocopheryl Phosphate in the Rat. K. L. Zierler, B. P. Folk, and J. L. Lilienthal, Jr. *Bull. Johns Hopkins Hosp.* 92: 26, 1953.

II. Effect on the Capacity of Rat Diaphragm to Dissimilate Hexose Phosphates. K. L. Zierler, R. Andres, R. I. Levy, H. M. Anderson, and J. L. Lilienthal, Jr. *Bull. Johns Hopkins Hosp.* 92: 32, 1953.

III. Inhibition of Insulin-Induced Glycogenesis in Isolated Rat Diaphragm. *Bull. John Hopkins Hosp.* 92: 41, 1953.

In this series of papers, Zierler and co-workers report their observations on the site of action of vitamin E in skeletal muscle metabolism.

Epinephrine activates phosphorylase, an enzyme involved in the conversion of glycogen to glucose-1-phosphate. The result is an elevation of blood sugar (from liver glycogenolysis) and an increase in blood lactic acid (from muscle glycogenolysis). When α -tocopheryl phosphate was administered to rats, epinephrine failed to produce the expected rise in blood lactic acid, although the hyperlycemic response was unaltered. The evidence suggests that α -tocopheryl phosphate suppresses muscle glycogen breakdown by limiting the availability of carbohydrate substrate for oxidation.

Further studies on isolated diaphragms furnished data that this effect of α -tocopheryl was mediated at the level of phosphoglucomutase. This is the enzyme involved in the step between glucose-1-phosphate to glucose-6-phosphate. Since this enzyme is also present in the liver, the authors postulate that the phosphoglucomutase system in the liver is different from that of muscle.

These interesting observations have to do only with one action of large doses of α -tocopheryl phosphate. How this effect is related to the physiologic activity of vitamin E in health and disease cannot yet be stated.—S. O. WAIFE

Folic Acid and Reproductive Efficiency. D. F. Lawson, C. N. DeGaris, and J. H. Bolton. *M. J. Australia* 1: 848, 1953.

On the assumption that a lymphocyte count of less than 1500/cu. mm. is presumptive evidence of folic acid deficiency, the authors noted the frequency with which this finding was seen in patients who had had bad obstetrical histories; that is, patients who had had miscarriages, unexplained stillbirths, premature births, etc. An absolute lymphocyte count was performed on 77 patients, of whom 21 were primigravidae and 56 multigravidae. Among the 56 multigravid women there were 145 untreated pregnancies, and 53 pregnancies during which the patient received folic acid for most or all of the prenatal period. When compared to a control group of 56 multigravidae with normal lymphocyte counts, it was noted that the incidence of miscarriage and premature births was significantly higher in the group not treated with folic acid and there was a marked improvement in the obstetrical outcome when folic acid was administered.

The authors state that folic acid therapy will not prove the answer for all patients with a bad obstetrical history. It also remains to be shown that the absolute lymphocyte count is a direct reflection of folic acid deficiency, or that the only difference in the two groups was the administration of folic acid.—S. O. WAIFE

Effect of DDD Treatment on Metabolic Response of Dogs to ACTH Injection. J. Nichols and H. D. Green. *Am. J. Physiol.* 176: 374, 1954.

ACTH was administered to dogs. They developed eosinopenia and diabetic glucose tolerance curves. The excretion of uric acid and allantoin was increased. When DDD (2,2 bis(parachlorophenyl)-1,1-dichloroethane) was administered for three weeks the inner zones of the adrenal cortex became atrophic while the outer zones were unaffected. At this time ACTH effects are blocked. Two possible explanations are suggested. The atrophic zones may be responsible for the formation of the hormones involved or the remaining outer zones are refractory to ACTH.—M. J. OPPENHEIMER

Differential Inactivation of Prolactin by Mammary Tissue from Pregnant and Parturient Rats. J. T. Sgouris and J. Mertes. *Am. J. Physiol.* 175: 319, 1953.

Inguinal mammary glands of rats were homogenized and incubated with prolactin. Following incubation, the tissues were assayed in White Carneau pigeons for prolactin activity. Mammary homogenates from lactating rats inactivated 65.6 per cent of the prolactin. Pregnant rats inactivated only 19.5 per cent. After corrections for milk content, it was shown that lactating glands removed eight times as much prolactin as pregnant ones. It is suggested that mammary glands of pregnant rats do not use prolactin. This factor contributes to absence of copious lactation during gestation.—M. J. OPPENHEIMER

Immediate Effect of X-Radiation on the Isolated Striated Frog Muscle. H. B. Gerstner, C. P. Powell, and E. O. Richey. *Am. J. Physiol.* 176: 9, 1954.

X-radiation up to 30 kr. produces no detectable effect on isolated muscle. Doses of 30–150 kr. immediately compromise function and produce changes in color, translucency, and length. Above 150 kr., function stops immediately and more pronounced changes develop of similar kind to those seen at 30–150 kr.—M. J. OPPENHEIMER

Reversal by DL-Methionine of Acute Effect of DL-Ethionine on Pancreatic Enzyme Output in Dogs. T. M. Lin and M. I. Grossman. *Am. J. Physiol.* 176: 377, 1954.

In anesthetized dogs amylase was secreted continually and undiminished for 6–9 hours under constant urecholine and secretin stimulation. An immediate fall in amylase output occurred when *dl*-ethionine was injected intravenously. After this, *dl*-methionine had no effect. However, the depressing effect of *dl*-ethionine was blocked by simultaneous or previous injection of *dl*-methionine.—M. J. OPPENHEIMER

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